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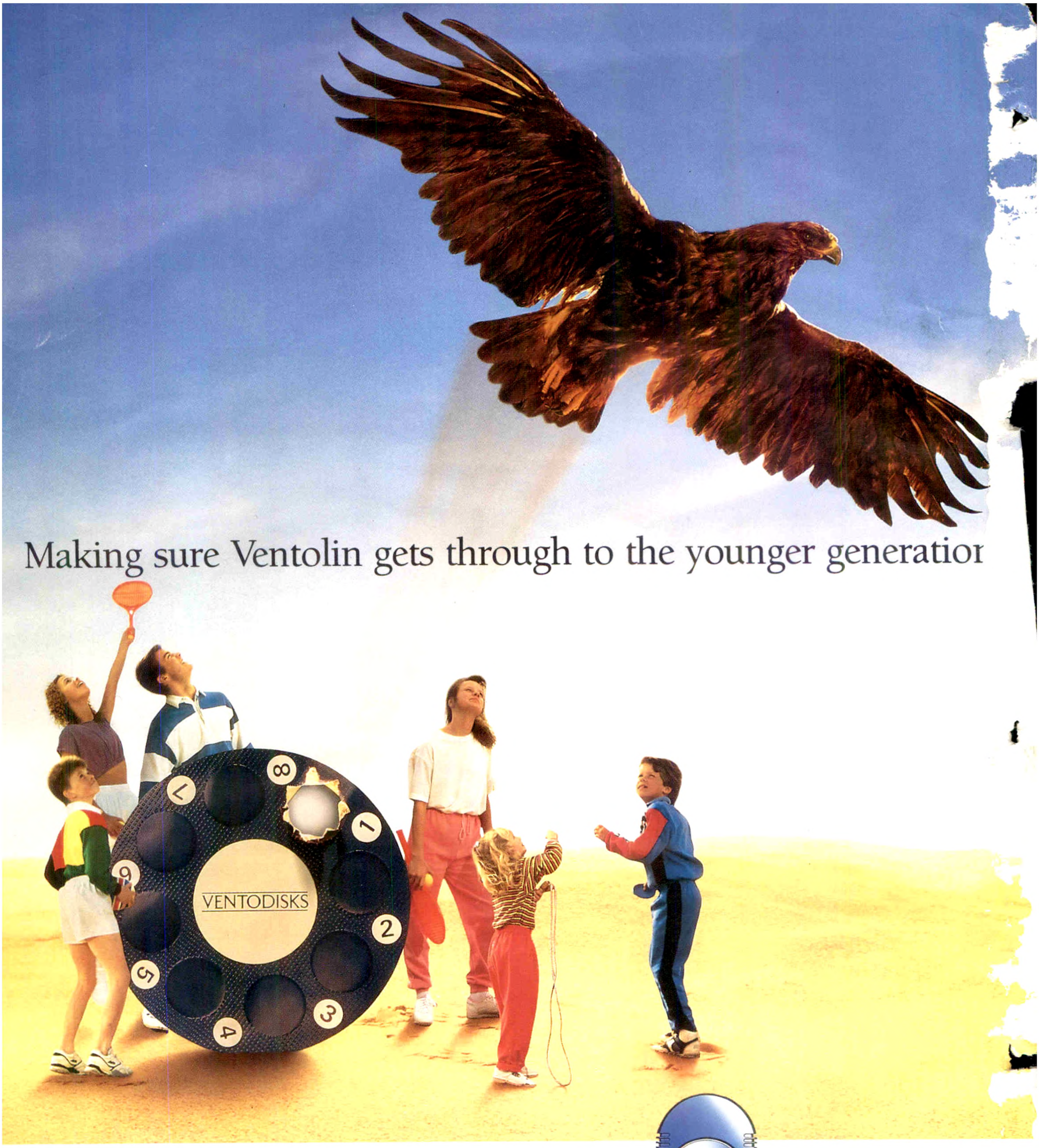
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The Journal of the British Paediatric Association

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JAMES SPENCE MEDALLIST 1991

Professor John A Davis

The James Spence Medal was presented to Professor John Davis on the 18th April 1991. Professor Dame June Lloyd, President of the British Paediatric Association, gave the following citation.

Professor John Davis

Imagine yourself a paediatric registrar. It is now 7 pm and you are walking home. You were up most of last night. It is cold and it is raining. Your professor is also on his way home. He stops. 'You will get terribly wet' he says kindly 'Let me give you a lift'. You would like to be able to accept but he has forgotten that today he is riding his bicycle.

This story, variously embellished, has been told on many occasions to illustrate John Davis' intense concern for others while at the same time demonstrating his absentmindedness and disregard of mundane practical matters. Had John been driving his car, however, our registrar might have had even more cause for anxiety. John has been reported to score alpha plus for dash and elan when behind the wheel but a flat gamma for anticipation of impending disaster or ability to reach his intended destination. Fortunately the James Spence Medal, of which John Davis is the 31st recipient, is not given for driving abilities or navigational skills. It recognises outstanding contributions to the advancement or clarification of paediatric knowledge and in these areas there can be no doubt about John's skills and pre-eminence.

John Allen Davis started his career with a London University Gold Medal, one of a very few paediatricians to have achieved this rare distinction. Shortly after graduation he did his stint in the army serving in Germany, and then came back to St Mary's to lay the foundations of his paediatric training. This took him from the wards of Paddington Green Children's Hospital over to the USA and to Boston; on his return, and even more importantly, he ventured out into the community around St Mary's where he contributed very greatly to that hospital's famous Home Care Scheme. It was in Paddington too that John came under the influence of Donald Winnicott, a great pioneer and leader in child psychiatry and himself a James Spence Medallist in 1968.

Many paediatricians have started their research career as Nuffield Research Fellows in Oxford. John is one of that band and he has made major contributions to our understanding of apnoea in the neonatal period, as well as in other aspects of newborn physiology. As a senior lecturer and subsequently reader at the Hammersmith Hospital he was a driving force behind the early development of neonatal intensive care. From the very beginning his contributions extended far beyond the physical difficulties of the sick infant in the cot and embraced the feeling of the family and the ethical issues facing family and staff alike. Everyone should read or reread his chapter on care of the newborn in the book he edited on ethical issues in neonatal intensive care.* There he reminds us that 'whatever is done should be done with what

---

*The book which Professor Davis jointly edited is *Parent-Baby Attachment in Premature Infants*.

can only be called reverence'. As Professor of Child Health in Manchester, where he enriched the life of that medical school over 12 important years, and then as Foundation Professor of Paediatrics in Cambridge, his influence spread even wider—always bringing ethics and philosophy as well as science to the bedside and expressing his ideas to a wider audience in the correspondence columns of journals and newspapers.

Within our Association John made his mark at an early stage; he became an Honorary Assistant Secretary in 1965, quickly moved to be Secretary of the Academic Board when that was founded in 1967, and later became the Board's Chairman. Out of office his wise counsels have continued and there can be few issues about which our files will not contain a letter from John Davis—with always a nugget of gold to be discovered once his dense and rather difficult handwriting had been deciphered. But if his handwriting is sometimes impossible to comprehend his speech certainly is not. As a lecturer John has few equals. I will always remember an hour long lecture on lipodystrophy that held the audience spellbound and was delivered without a note and with relatively few slides. When I congratulated him afterwards he said 'If you can't talk without having mastered your script you shouldn't be speaking'. Those who have learnt most from John, however, will agree with Angela Rumbold, Minister of State at the Home Office, who recently wrote that she learnt more at her parents' dinner table than from her numerous schools. The table that John and Madeline kept in the kitchen of their home was where John's best teaching was done.

I cannot end without mention of what is probably his major and most enduring contribution to the science of our subject. His editorship with John Dobbing of that great book *The Scientific Foundations of Paediatrics* will always serve to remind us of his place in the development of our discipline. The preface to the first edition tells us that the book is—and I quote 'dedicated to R A McCance, Ronald MacKeith, Mary Sheridan and Donald Winnicott—all of them James Spence Medallists of the British Paediatric Association who, in their several ways, have been responsible for reminding British paediatricians that their primary concern should be with growth and development and its relationship to medical practice'.

In joining this distinguished band John Davis reminds us above all that growth and development concerns not only the body but also the mind and the spirit.

John Spence Medallists

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1963	Sir F Macfarlane Burnet
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1967	Professor R R A Coombs
1968	Dr Mary Sheridan
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Annotation

Effects of parental divorce on children

Though divorce rates have been more or less stable in Britain over the past decade and the steep increases of earlier years have levelled off, concern about the consequences of divorce for both adults and children has remained high. There is continued interest too in practical responses. Conciliation services are now an established part of the scene, albeit very inadequately supported financially, and are developing a wide range of approaches.[1] There is also the prospect of a new divorce law which is intended to encourage negotiated settlement of conflicts.

The distress and difficulties that children experience as they become aware that their parents may separate, and which persist through the often long and drawn out process of divorce, have been well described.[2–4] Research has made a good deal of headway in identifying the factors which are important for children's adjustment. Where children maintain good relationships with both parents the negative effects of divorce are mitigated. But breaks and continuing change in these relationships can be associated with low self esteem, depression and anxiety, acting out behaviour, and poor relationships with peers.[5–7] Continuing conflict between the parents after a divorce has also been found to result in negative outcomes for children possibly because the conflicts tend to erode the quality of parent-child relationships.[8] Joint custody arrangements have often been promoted as helpful to children and, although research evaluation is still far from adequate, the indications are that it is helpful insofar as it may help to maintain good relationships between the child and both parents.

Parental health often suffers as a marriage ends.[9] Poor health and particularly poor psychological health may reduce the capacity to be an effective parent, and this may also be an important factor in children's adjustment.

Research in both Britain[10] and the USA[11] has drawn attention to the sharp drop in income to households with children after divorce. Probably the majority of the poorest homes with children in Britain have been created through a divorce and, of course, as is well known, poverty has very detrimental effects on the development of children. Government plans 'to make fathers pay' seem unlikely to have a significant effect on the situation as the main consequences would seem to be to create a net flow of money from fathers to the exchequer.

There is growing research interest in the effects of remarriage on children, but we are still some way from obtaining a consistent picture. Though household incomes will tend to rise with remarriage, the arrival of a new adult may bring further difficulties for children and exacerbate their behavioural problems.[12 13] Some of this effect may arise because remarriage is usually associated with a reduction in contact with the non-resident parent.[14]

Increasingly divorce researchers are moving away from the smaller scale, more clinical studies, to larger more representative samples. Although these provide better grounded evidence about outcomes, the lack of detailed information about family relationships makes the interpretation of some findings difficult. Allison and Furstenberg have analysed data from the 'National Survey of Children' (a nationally representative sample of 1197 children in the USA).[15] Their results suggest that marital dissolution has negative and longlasting effects on behaviour, psychological wellbeing, and academic performance. In magnitude, the effects were found to be slightly smaller than sex differences (so that for example the difference between boys and girls on measures of academic performance is slightly larger than the difference between those with married parents and those with separated/divorced parents), but larger than those associated with other demographic variables such as mother's education.

In contrast to many other studies, Allison and Furstenberg found no evidence that boys were more affected by their parents' divorce than were girls. There was, however, evidence that effects were larger for those children who were very young at the time of their parents' separation. This finding is consistent with that of Wallerstein and Kelly, whose detailed interviews with the parents and children from 60 divorcing families in California also suggested that younger children (3–5 years of age) have particular difficulty adjusting to parental divorce because their limited cognitive capacities prevent them from fully understanding the meaning of the divorce.[2] This can lead to fear of abandonment, unusual fantasies, emotional neediness, and behaviour problems.

Perhaps the best sources of British data with which to examine the effects of parental divorce on children are the national cohort studies. The National Child Development Survey, which is a cohort study of all the children born in Britain in one week of March 1958, had followed up children from their birth, with data collected at age 7, 11, 16, and most recently at age 23. Of the original cohort of around 17 000 births, approximately 700 children had experienced parental divorce before the age 16 data collection.

The longitudinal nature of the data has enabled us to analyse the children's behaviour and educational performance both before and after the parental divorce.[13] These analyses suggest tht some of the problems for children that have previously been attributed to parental divorce or separation may in fact be present before the separation. Measures of mathematics and reading ability and measures of disruptive behaviour and unhappy and worried behaviour have been used on children at age 7 and at age 16. It was found that both boys and girls whose parents divorced when they were between 7 and 16 years old obtained worse scores on each of these four measures both at age 16, after the divorce, and also at age 7 before the divorce (in many cases several years before), and while the parents were still living together.

Most, but certainly not all, divorces are preceded by a period of marital conflict and this has been found to be associated with behavioural problems in children.[16] But there are several other possible explanations for our results. For instance, it has been suggested that adults with poor psychological health are more likely to separate. Or the growing marital problems may have negative effects on parent-child relationships.

The cohort of children born in one week in 1946 (The

National Survey of Health and Development) has been followed up from birth to age 36 and analyses suggests that some effects of parental divorce may persist into adulthood. The effect of divorce on educational achievement results in an increased likelihood of children leaving school without qualifications and an appreciable reduction in their chances of entering higher education. Not surprisingly there are also indications of reduced earnings and occupational status in adulthood.[17] The lower educational achievement is also apparent in the 1958 cohort. There are also indications from analyses of the 1946 cohort of a slight increase in the probability of divorce in young adulthood, perhaps associated with a tendency towards earlier marriage.[18]

There is little doubt that parental divorce can be a major disruption in children's lives that for some has long term consequences. But with the growth of services that aim to help parents settle their differences at divorce there is some hope that such effects may be reduced for future generations, particularly if these were coupled with more effective means of reducing the poverty that divorce brings for too many children.

B JANE ELLIOTT
MARTIN P M RICHARDS

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1. Livingston J *et al* (1989) Br J Clin Pharm 27 (Suppl 1): 1095 –1125

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Preschool vision screening in Cornwall: performance indicators of community orthoptists

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Abstract

The performance of community orthoptists was retrospectively assessed in a primary preschool screening programme that has been established in Cornwall since 1982. The outcome of screening was compared between random samples of two birth year cohorts corresponding to the second and fourth years of existence of the screening programme (1980, n=298 and 1982, n=300). The mean age at screening was significantly later for the second cohort (4·3 years compared with 4·4 years) but otherwise performance indicators improved in the second cohort.

Community orthoptists achieved a sensitivity of about 90% and specificity of 99% during the study. It is unlikely that the more commonly used two tier system of health visitors referring to a community orthoptist could achieve this degree of accuracy.

A preschool vision screening programme was established in Cornwall in 1982 to screen all children over 3·5 years of age living in Cornwall for visual deficit or strabismus or both. The aim of this paper was to assess the performance of the community based orthoptists who are responsible for carrying out this primary screening programme. The results of treatment of those children screened positive are presented elsewhere.

The purpose of the preschool vision screening programme is to identify children with small squints or amblyopia (or both), either strabismic or refractive, while there is still hope of treating the condition successfully, and to identify and correct any refractive error so that any visual disability is minimised before schooling begins.

It is clear from the Hall report[1] and from a paper by Stewart-Brown *et al*[2] that the cost effectiveness of preschool vision screening has never been proved. Many different approaches to the vision screening of children are used, and I know of little evaluation of results. Although there are a number of papers presenting the results of primary preschool vision screening by community orthoptists no formal appraisal of their performance has been published.[3–9] In particular, I could find no record of any attempt to assess the sensitivity of this screening method, perhaps because of the difficulty of determining the number of children missed by screening.

With one county border and fully centralised ophthalmic and community paediatric services, Cornwall was geographically ideal for a population based analysis of the outcome of preschool vision screening.

Subjects and methods

ORGANISATION OF PRESCHOOL SCREENING

Children are identified from a computerised register into which they are entered at birth and invited to attend for screening. The register produces a printout of the names of children attaining the age of 3·5 years (when they become eligible for screening), which is sent to the screening office every few months. The register is updated by health visitors for children who enter or leave the county. The parents or guardians of eligible children are sent one invitation only for preschool vision screening, which takes place at the nearest of the 22 clinics throughout the county. Confirmation of attendance is not required, but a request is made to change or cancel the appointment if necessary.

The history and examination (which take about 10 minutes if the child is cooperative) are standard and the following are noted:

- Distance vision measured on Snellen chart at 6m with card (Sheridan Gardiner chart at 6m or Kay pictures are used when cooperation is poor)
- Head posture
- Convergence to nose
- Cover test, near and distance, Prism cover test: 20 dioptre base out (occasionally 10)
- Ocular movements: nine positions of gaze
- Stereoscopic vision: Wirt fly test and pictures of animals.

Criteria for referral of a child to hospital are: inability to see the 6/9 line on the Snellen chart with either eye, or inward or outward deviation on cover test (>8 prism dioptres), or both. Any child with an obvious squint or other clinical abnormality is referred.

Children with detected abnormalities are referred directly to the ophthalmologist and a note is sent to the patient's general practitioner. If there is doubt about the abnormality, a follow up appointment can be made within the preschool vision screening service.

METHOD OF EVALUATION

Two birth year cohorts were selected to assess the performance of the screening programme—children born in 1980 who are eligible for screening by mid-1983, and those born in 1982 who became eligible by mid-1985. In this way the performance during the second and fourth years of the screening programme was assessed. All children who lived in the northern and eastern ends of the county and who would normally be referred to Plymouth were excluded to facilitate retrieval of information from hospital records. Two approaches to the evaluation of outcome were made for each birth year cohort.

Firstly, a random sample of 300 children eligible for screening from each birth year cohort was taken directly from the computer printout used to invite children for preschool vision screening. Screening record cards for each selected child were drawn from the file and details of findings and outcome entered on to a microcomputer database.

This information allowed estimates of attendance rate, referral rate, and mean age at the time of screening for each birth year cohort.

To gain some information about why some children did not attend, a sample of non-attenders were asked questions by telephone. Records at the department of child health were scrutinised to identify the proportion of non-attenders who had changed their addresses or moved out of the county.

Secondly, another database was made from the record book at the department of child health of all the children referred from both birth year cohorts. A third database was made from a similar record of all children from the two birth year cohorts who were referred with visual abnormalities that had been detected by school medical officers soon after the children had started school; this database included the reason for referral and result of preschool vision screening.

The specificity of the primary screen by community orthoptists was calculated from the number of children referred to hospital who were found to be normal by the hospital orthoptist and consultant ophthalmologist.

The sensitivity of screening was calculated from the number of children with true abnormalities that had not been detected at the preschool vision screening (refractive error, strabisms, strabismic or refractive amblyopia) who were referred by the school medical officer. Only those children who attended preschool vision screening and who were later seen by a school medical officer were included. Non-attenders and those children who had subsequently moved into the county or who were not listed (and hence not invited to preschool vision screening) were excluded from the calculation of false negative results of preschool vision screening. Some false negative results may have been missed, because the school medical officer may also have failed to detect any abnormality. The pattern of school medical officer referral by school medical officers did if anything err on the side of caution, as there was a high false positive rate; it is unlikely, therefore, that many were missed. In addition, a number of children may have developed abnormalities between attending preschool vision screening and going to school thereby being wrongly classified as false negatives. The number of these is also likely to be small and any error arising from either of these sources will counteract itself. Finally, we calculated the predictive value of a positive screening result.

Results

RANDOM SAMPLE

The number of children sampled from each cohort was: 1980—total 4128, 298 sampled (7·2%), 145 boys and 153 girls; and 1982—total 3797, 300 sampled (7·9%), 155 boys and 145 girls. There was no significant difference in attendance or referral rates between the cohorts (table 1).

The mean ages at the time of screening were 4·25 years for the 1980 cohort and 4·42 years for the 1982 cohort. The probability that this difference was a chance finding as a result of a sampling error was <0·001 (Student's *t* test).

Of the total sample of 598, 157 did not attend. About half the total sample were still at the same address in 1988, 42% had moved (12% out of the county), and no information was available for 8%. Only 20% of the non-attenders had telephone numbers in the local directory, which might indicate a socioeconomic influence on attendance. Of 29 phone calls made, the commonest reason for non-attendance was no recollection of receiving an appointment (n=14), followed by no appointment received (n=6), already receiving treatment (n=6), and already attended and screen normal (n=3).

REFERRALS AFTER PRESCHOOL VISION SCREENING

The actual referral rates compare well with the sample estimates of 3·7% for the 1980 cohort and 5·3% for the 1982 cohort being 3·9% and 4·6%, respectively. Of the 159 referred from the first cohort there were 93 boys and 66 girls, and of the 176 referred from the second cohort there were 92 boys and 84 girls.

Table 2 lists the defects for which children were referred from both cohorts, including the false positives. Only three of the 20 squints referred by the community orthoptists from the 1980 cohort had been misdiagnosed. There were no false positive squints in the 1982 cohort.

REFERRALS BY SCHOOL MEDICAL OFFICERS

Many more children were referred by school medical officers from the 1980 cohort: 1980, 134 and 1982, 69 (total 203). This includes all children referred by school medical officers.

Table 1 Data of each birth year cohort with 95% confidence intervals (CI)

	1980 cohort (n=298)		*1982 cohort (n=300)*	
	No (%)	*95% CI of %*	*No (%)*	*95% CI of %*
Attenders:				
Total No	198 (66)	61 to 72	204 (68)	63 to73
No referred	11 (4)	2 to 6	16 (5)	3 to 8
Did not attend	82 (28)	23 to 32	75 (25)	20 to 30
Others:				
Total No	18 (6)	3 to 9	21 (7)	4 to 10
Already being treated	6 (2)	0·5 to 4	6 (2)	0·5 to 4
Refused or moved away	12 (4)	2 to 7	15 (5)	3 to 8

Table 2 Defects found at screening by orthoptists that lead to referral in each birth year cohort

Defect	*1980 (n=298)*		*1982 (n=300)*	
	Total No	*No of false positives*	*Total No*	*No of false positives*
Reduced vision in one eye	78	6	104	5
Reduced vision in both eyes	59	1	57	3
Convergent squint	6	1	3	0
Divergent squint	1	0	1	0
Reduced vision in one eye and convergent squint	8	0	5	0
Reduced vision in both eyes and convergent squint	4	0	4	0
Reduced vision in both eyes and divergent squint	1	1	0	0
Other	2	1	2	0
Total	159	10	176	8

Table 3 Defects that resulted in referral by school medical officers in each cohort by outcome of preschool vision screening

Defect	*No abnormality found at preschool vision screening*		*Did not attend preschool vision screening**		*Not listed*	
	1980	*1982*	*1980*	*1982*	*1980*	*1982*
Reduced vision one eye	12	2	13	11	11	4
Reduced vision both eyes	14	5	18	12	18	4
Convergent squint	3	2	2	4	2	1
Divergent squint	3	6	3	2	1	0
Esophoria	0	1	0	0	0	0
Reduced vision one eye and convergent squint	0	0	1	0	0	1
Reduced vision both eyes and convergent squint	0	1	1	0	1	0
Other	1	2	1	2	0	0
Normal vision recorded as 6/9 or better in both eyes by school medical officer	15	6	11	1	3	2
Total	48	25	50	32	36	12

*Includes nine children whose preschool vision was unknown.

Table 4 Referrals after preschool vision testing and by school medical officers in each birth year cohort

	1980 (n=298)		*1982 (n=300)*	
	No	*% Of total referred*	*No*	*% Of total referred*
Referred after preschool vision screening				
True positive	143	69·1	151	75·1
Did not attend	6	2·9	17	8·5
False positive	10	4·8	8	4·0
Total	159	76·9	176	67·6
Referred by school medical officers				
False negative preschool vision screening	21	10·1	12	6·0
False positive referral by school medical officers	25	12·1	11	5·5
Did not attend	2	1·0	2	1
Total	48	23·2	25	12·5
Total referred	207	100	201	100

Only 73 of them had been passed as normal at preschool vision screening, and 21 would have passed as normal by preschool vision screening referral criteria (they had 6/9 vision or better in either eye with no deviation on cover testing). The reasons for their referral was not apparent. Fifty two children, therefore, had potentially false negative diagnoses on preschool vision screening, and 33 were found to have defects.

The number of defects detected by school medical officers for all children born in 1980 and 1982 are listed in table 3 including the findings for those who did not attend for preschool vision screening and for those who were not listed and consequently not invited to preschool vision screening. A large number of divergent squints was detected by the school medical officers, all of which were false positives. The prevalence of defects among the non-attenders is similar to that among the attenders suggesting that there was no significant attendance bias in either direction. The number of unlisted children was much higher for the 1980 than the 1982 cohort (36 compared with 12).

SENSITIVITY AND SPECIFICITY

Table 4 summarises the true and false positive results of preschool vision screening, the false negatives for preschool vision screening (true positive referrals by school medical officers), and the false positive referrals by school medical officers. Also included is the number of children referred who failed to attend hospital (3·9% for the 1980, and 9·5% for the 1982 cohort); it is impossible to state whether they should have been referred.

Table 5 shows the sensitivity and specificity calculations for each cohort. The number of true negative results must be estimated from the attendance rate of the sample, and consequently a range is given that includes the 95% confidence interval (CI) around the sample estimate.

Table 6 shows the sensitivity, specificity, and predictive value of preschool vision screening for each cohort.

Table 5 Calculation of sensitivity, specificity, and predictive value of preschool vision screening for each birth year cohort.

Screen result	*Referral outcome*		*Total*
	Abnormal	*Normal*	
1980 Cohort			
Positive	143	10	153
Negative	21	2352 to 2778	2373 to 2799
Total	164	2362 to 2788	2526 to 2952
1982 Cohort			
Positive	151	8	159
Negative	12	2217·5 to 2602·5	2229·5 to 2614·5
Total	163	2225·5 to 2610·5	2388·5 to 2773·5

Table 6 Sensitivity, specificity, and predictive value (%) for preschool vision screening for each birth year cohort

	1980	*1982*
Sensitivity	87·2	92·64
Specificity	99·58 to 99·64	99·64 to 99·69
Predictive value:		
Positive	93·46	94·96
Negative	99·12 to 99·25	99·46 to 99·54

Discussion

This paper shows that in this setting, community orthoptists are efficient and accurate primary screening personnel.

There are many aspects to the full evaluation of a screening programme. These include measures of both process and outcome, as well as of cost effectiveness. This must take into account diverse marginal costs in addition to the costs of detecting and successfully treating a case, compared with the cost to the individual subject and community of failing to do so. Only measures of outcome of the performance of this screening programme are considered in this paper.

Children undergo numerous screening procedures for conditions that vary greatly in their severity and prevalence. Visual deficit has for a long time been regarded as a disability worthy of early detection and intervention, and is generally regarded as an important public health problem.[10] There is little evidence that disability arising from unilateral amblyopia, be it strabismic or refractive, is of any importance except when there is blinding injury or disease in the seeing eye. There is also little evidence that children with profoundly amblyopic eyes can be successfully treated. This is exemplified by Ingram, who no longer advocates the early screening of children for visual deficit, and now seems to doubt the efficacy of treatment of children with more severe amblyopia.[11–14] Other authors have reported some benefit from screening although not in properly controlled studies.[15–17]

For a disease to justify population screening, it must be shown that treatment is both tolerable and effective, at least in most cases.[18] This aspect will be dealt with in greater detail elsewhere. The results of treatment are not remarkable, with a mean improvement of only one line on a Snellen chart for the whole group. The main determinant of successful outcome of treatment is the severity of amblyopia at the time of screening; age does not significantly influence outcome.

This study provides estimates of the outcome measures of the community orthoptists as primary screeners and the sensitivity, specificity, and predictive value are good, as they should be when the personnel have been specifically trained to detect visual abnormalities in small children. The performance of community orthoptists as primary screening personnel should be compared with results using health visitors as primary screeners and community based orthoptists as secondary screeners to whom children with possible abnormalities or who are thought to be at high risk are referred. Unfortunately there are no published studies with which an adequate comparison can be made. The figures for sensitivity, specificity, and predictive value would be hard to match in a two tier system, as would the much greater efficiency of a single tier system. We do not know the difference in cost between setting up and administering a dedicated primary preschool vision screening programme using community orthoptists and a two tier system.

One way of answering these questions would be to carry out a randomised trial of screening in a district in which a two tier primary programme is in operation. Children should be randomly selected to primary screening by a community orthoptist or to the existing health visitor based screening. The cost and logistics of the two approaches should be compared, as well as the measures of process and outcome. Alternatively, if it cannot be shown that health visitors are able to achieve a comparable level of performance, it is reasonable to conclude that community orthoptists are the most effective people to carry out the screening.

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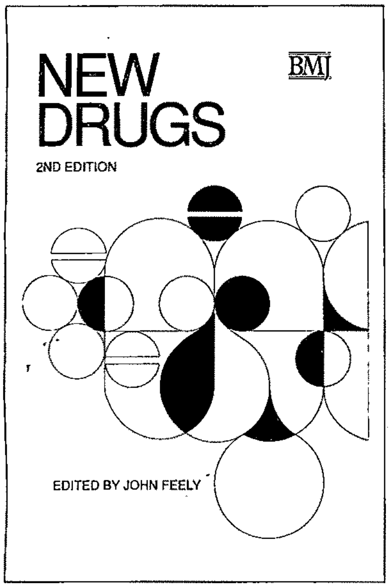

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Audit from preschool developmental surveillance of vision, hearing, and language referrals

R J Rona, A Reynolds, M Allsop, R W Morris, M Morgan, S Mandalia

Abstract

Referrals from preschool medical examinations were followed up for two years to assess attendance rate, waiting time for appointment, appropriateness of the referral, the diagnosis and management of the condition. Altogether 184 children were referrals for ophthalmology, 285 for audiology, and 195 for speech therapy. The median waiting time for an appointment was 46 days in ophthalmology, 175 days in audiology, and 83 days in speech therapy. The poorest attendance rate was identified in speech therapy (75%). Approximately 60% of examined children had a justified referral to ophthalmology and 20% had a clear defect. Over half the children in audiology (55%) had an altered impedance or hearing impairment. Of those with a hearing problem kept under review only half improved spontaneously. In speech therapy 80% of those assessed had a language problem. Many health problems were detected for which parents were unaware or did not use the service. Parental awareness alone will not uncover the sizable level of lingual and sensorial problems in inner city areas. This audit identified specific deficiencies in the provision of services and a number of organisational changes are suggested to improve their effectiveness.

The joint working party on child health surveillance was sceptical of the effectiveness of many of the scheduled prescribed examinations in Britain and recommended research to evaluate the current components of the programme.[1] The group was particularly critical of the assessment of squint by non-specialised personnel, visual acuity before school age, universal hearing screening after 10 months until school entry, and systematic assessment of language problems. In West Lambeth Health Authority an audit programme was carried out to assess whether the child examination schedule provided by clinics was operating efficiently. We were concerned to describe the actions which took place after a child was identified as having a sight, hearing, or language problem. Areas of ascertainment were the level of attendance to the specialist services, waiting time for appointment, the appropriateness of the referral, the diagnosis, and treatment of the referred children and the compliance with the prescribed treatment. No formal audit of these services has been carried out previously in Britain. The study should be relevant to health districts with multiethnic inner city area characteristics.

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Subjects and methods

All the children aged under 4·5 years of age referred to speech therapy, audiology, or ophthalmology as a result of a scheduled examination were flagged and followed up for a two year period from August 1986. A general information document was completed by the referring clinical medical officer or health visitor and three specific documents relating to each specialty were designed to be completed by the research assistant (AR) based on information obtained from the notes and directly from the specialists. The data were recorded on a precoded form for each child at six, 12, and 24 months after referral or at discharge if this occurred before the follow up dates.

The general information document based on the examination by the clinical medical officer or health visitor recorded date of birth and sex, area of concern, specialty to which the child was referred, and whether the referral was initiated by the doctor or health visitor. The clinical medical officers used scheduled examination tests for assessment. For hearing they used the distraction test at 7 months, the Stycar 6 toy test at age 2 years, and the Stycar 7 toy test at age 3·5 years. The receptive and expressive language was examined using a modification of the tests used in the Hounslow study[2] and approved by Reynell. Vision binocularity was assessed with the corneal reflection test, cover test, and eye movement at each examination and Stycar 5 letter test at 3·5 years. (This test is known to be insensitive to amblyopia so the recently developed Sonksen-Silver linear test for 3 m is used now.) All the clinical medical officers have undergone in service training, but the techniques of screening were not systematically checked during the study period.

Information from the specialists to whom the children were referred was recorded for the following items for each specialty. (1) At first assessment the attendance and, if appropriate, reasons for non-attendance, date of initial assessment, findings of initial assessment, and management plan. (2) At the second and third assessment details of most recent examination and type of management carried out since the last follow up, for example, surgery, visual aids, treatment, etc. For audiology, hearing impairment and impedance were assessed over the two year period. Language, mouth, voice, articulation, and fluency problems were assessed. In addition the Reynell test was used to measure language comprehension and expressive language. The number of treatment sessions with the speech therapist was recorded. The ophthalmology information on binocularity, refractive problems, vision acuity with corrective aids, if available, amblyopia, and other pathology were recorded.

We aimed to collect at least 180 children in each specialty. Data were collected for seven months in audiology (which had the highest referral rate), eight months in ophthalmology, and 11 months in speech therapy.

Results

Table 1 gives the age on referral, date, and sex distribution of children referred to three specialties. Altogether 184 children were referred to ophthalmology, 285 to audiology, and 195 to speech therapy. Appreciably more boys were referred to speech therapy than girls. In ophthalmology proportionally more children were referred who were under 1 and over 3 years old. In audiology proportionally more children were referred in the younger age groups whereas for speech therapy, with the exception of one boy, specialist opinion was required after the child's first year of life. Multiple referrals in the three specialties of interest were detected for 38 children referred to audiology and speech therapy, 13 referred to audiology and ophthalmology, seven referred to ophthalmology and speech therapy, and four to the three specialties. The referral rates for the three specialties were approximately 10% in audiology, 6% in ophthalmology, and 4% in speech therapy. The referral rate in speech therapy may have been underestimated because unlike the other two specialties there was a lack of a centralised administrative system making cross checking of referrals difficult.

Figure 1 shows the main process events of the referred children during the two years follow up. Compliance, defined as attending the specialised clinic at least once, was 79·9%, 75·1%, and 63·6% of children referred to ophthalmology, audiology, and speech therapy respectively. Some children had predicted reasons for non-attendance such as change of address, parental refusal at invitation stage, or children already undergoing assessment by the service. Between 3·3% and 5·6% of the flagged referrals were not traced in the specialised clinics. The true non-attendance was 15·2%, 17·2%, and 25·1% in ophthalmology, audiology, and speech therapy respectively. Approximately a quarter of all referred children were discharged in ophthalmology and audiology after first assessment and the equivalent percentage in speech therapy was 10·8%. In addition, around 15% of the children in ophthalmology, 18% in speech therapy, and 8% in audiology did not attend the

Table 1 Age and sex distribution of referred children by specialty referred to. Results are number (%)

Age (years)	*Ophthalmology*		*Audiology*		*Speech therapy*	
	Boys	*Girls*	*Boys*	*Girls*	*Boys*	*Girls*
<1	31 (37·3)	45 (44·6)	60 (38·7)	53 (40·8)	1 (0·8)	0
1–2·9	18 (21·7)	23 (22·8)	69 (44·5)	50 (38·5)	66 (54·1)	50 (68·5)
≥3	34 (41·0)	33 (32·7)	26 (16·8)	27 (20·8)	55 (45·1)	23 (31·5)
Total	83 (100·0)	101 (100·0)	155 (100·0)	130 (100·0)	122 (100·0)	73 (100·0)

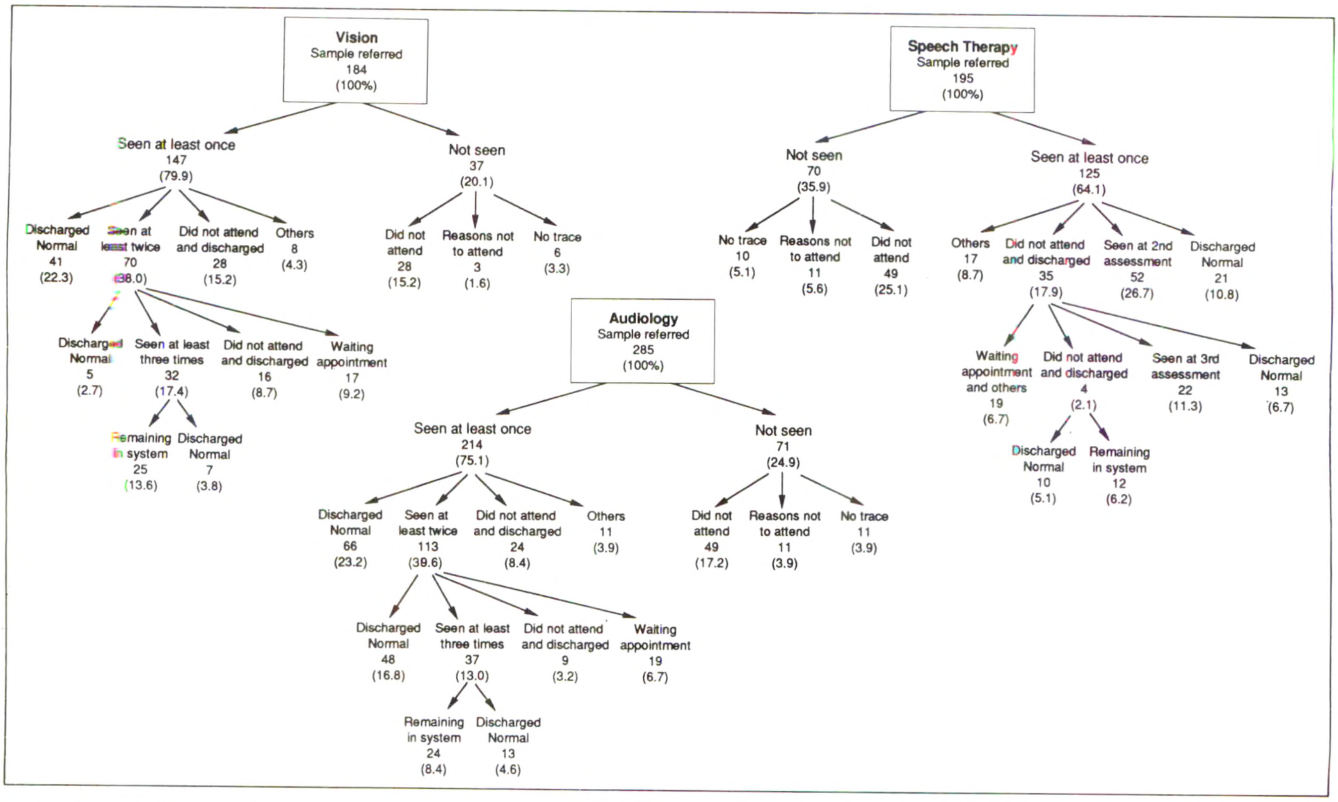

Figure 1 Compliance with specialist clinic and process events of referred children.

specialised clinic after first assessment. At the end of the two years' follow up, approximately 42 (22·8%) children were still in this system in ophthalmology and 43 (15·1%) in audiology and in speech therapy there were approximately 25 (12·9%) children.

The waiting time for first assessment varied by speciality. For vision the mean time was 62·7 days (median 46 days), for audiology a mean of 179·8 days (median 175 days), and for speech therapy a mean of 88·5 days (median 83 days).

OPHTHALMOLOGY

Table 2 gives the initial assessment of diagnostic events by age in ophthalmology. There were 66 children for whom no problem has yet been identified. For most children aged less than age 2 years visual acuity was not assessed. Strabismus was detected in 13 children and most of them had a non-paralytic squint. In another 45 children no squint was found but there were reasons for the clinical medical officers to suspect a squint (either pseudosquint or family history). Two children were diagnosed at a later stage as having a non-paralytic squint and another child initially said to have an accommodative squint had his diagnosis changed to normal. Twenty three children had a refractive problem, seven had hypermetropia, six had hypermetropia astrigmatism, three myopic, five myopic astigmatic, and two were astigmatic. Visual acuity defects were detected in nine children including one line difference in visual acuity between right and left eye but excluding a bilateral visual acuity of 6/9. At a later assessment another three children had developed decreased visual acuities that were not detected initially. Thus the referral was justifiable in 55% of the children. Table 3 gives the number of children with at least one ophthalmic problem and the number of children in each group treated. Of the 29 children with an ophthalmic problem 20 were given treatment. Most children with a refraction and visual acuity problem were treated but five out of six children with squint only were left under observation. Of the children with a refractive problem 14 were treated with glasses and four with occlusion and glasses.

There seemed to be no consistency in the discharge policy of the ophthalmology clinic. For example 10 of the 31 children with pseudosquint were discharged immediately and seven were discharged after a second assessment but 12 of the children remained in the system until the end of the study. The same phenomenon was observed for mild visual problems (6/9) and at risk of squint. Of those children given treatment compliance was good in 14, poor in four children, and unknown in two children. Outcome assessment of treatment was not possible given the small number of children in each diagnostic category.

Table 2 Diagnostic events of children referred to ophthalmology by age

	Age (years)			All
	0–0·9	*1–2·9*	*3–4.9*	
Binocularity:				
Non-paralytic	4	3	2	9
Accomodative	1	1	2	4
Pseudosquint	21	8	2	31
Family history	10	—	4	14
Refractive problem alone	6	5	12	23
Visual acuity:				
Bilateral 6/9	N/A	3	10	13
One line difference	N/A	2	2	4
Two lines difference	N/A	1	2	3
Bilateral 6/12	N/A	—	2	2
Unknown	2	1	—	3
No abnormal findings	24	14	28	66

N/A=not applicable as it was not tested.

Table 3 Number of children with at least one ophthalmic problem in the initial assessment and whether a treatment was prescribed

	No of children	*No treated*
Squint only	6	1
Refraction problem only	9	7
Squint and refraction defects	6	4
Refraction and visual acuity defects	7	7
Squint, refraction, and visual acuity defects	1	1
Total	29	20

AUDIOLOGY

Table 4 gives information about initial assessment and action taken in the audiology clinic. In general children referred from audiology to the ear, nose, and throat department or the general practitioner had a flat impedance trace and a moderate or mild hearing impairment. On the other hand most children discharged after first assessment had normal hearing and impedance tests, only five were discharged with a mild hearing impairment, and one with a flat impedance test. In the group who continued under review there was a large percentage of children with apparently similar results to those referred to ear, nose, and throat or the general practitioner. Twenty children with a flat impedance had either a moderate or mild hearing

Table 4 Tests results and action taken after initial assessment in audiology clinic (hearing loss graded severe, moderate, mild, normal, based on worse ear)

Action after first assessment	*Impedance*																	
	Flat					*Slight alteration*				*Normal*				*Not tested*				
	Severe	*Moderate*	*Mild*	*Normal*	*Not tested*	*Moderate*	*Mild*	*Normal*	*Not tested*	*Moderate*	*Mild*	*Normal*	*Not tested*	*Moderate*	*Mild*	*Normal*	*Not tested*	*Total*
Ear, nose, and throat	—	4	5	—	4	—	1	—	—	—	—	—	—	—	—	—	—	14
General practitioner	—	6	16	—	1	—	3	—	1	—	—	—	—	—	—	—	—	27
Other	1	—	—	—	2	—	1	—	3	—	—	1	3	—	—	—	—	11
Under review	—	2	18	1	4	3	26	4	7	5	19	1	5	—	1	—	—	96
Discharged	—	—	—	—	—	—	1	7	6	—	3	20	24	—	1	3	1	66

defect and another 29 had a hearing impairment and slightly abnormal impedance. The action decided was not related to hearing impairment being bilateral or unilateral as most children had bilateral hearing impairment. Too few children required referral to sensorineural evaluation for helpful analysis.

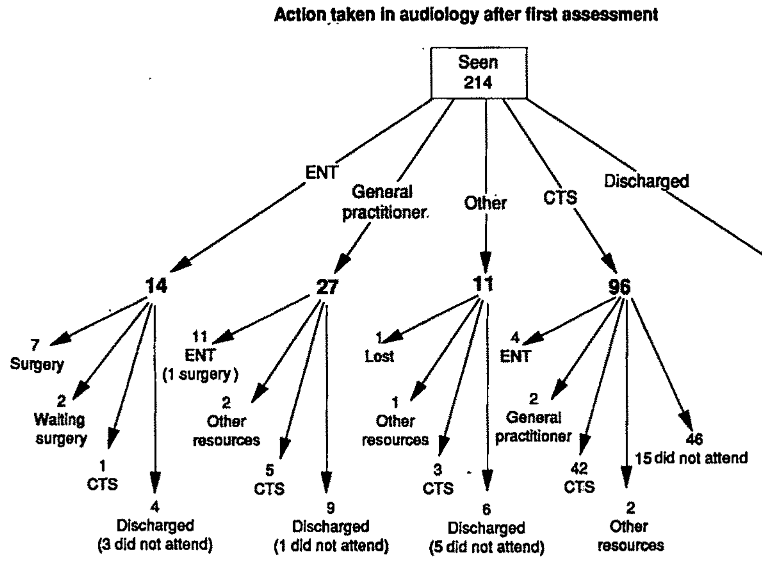

Figure 2 Action taken in audiology after first assessment. CTS=continued to see; ENT=ear, nose, and throat department.

Table 5 Referral to speech therapy according to number of language problems

	Age at referral (years)				Total	
	1·0–2·9		3·0–4·9			
	Boys	Girls	Boys	Girls	Boys	Girls
No problem	4	6	5	4	9	10
One problem:						
Moderate or severe	4	1	8	2	12	3
Mild	4	4	6	1	10	5
Two problems:						
Moderate or severe	17	12	5	2	22	14
Mild	4	6	4	2	8	8
Three problems:						
Moderate or severe	6	3	2	4	8	7
Mild	1	1	—	—	1	1
More than three problems	—	1	—	—	—	1
Incomplete assessment or not known	3	3	—	—	3	3
Total	43	37	30	15	73	52

Figure 2 shows a flow chart of eventual action in relation to initial decision. Half of the children sent to the ear, nose, and throat department had surgery by the end of the follow up period. Approximately 40% of the children sent to the general practitioner were subsequently referred to the ear, nose, and throat department. Of those children who remained under review after initial assessment half of them were discharged or did not attend subsequent appointments, 6% were sent to the ear, nose, and throat department or their general practitioners, and 44% were still under review at the end of the follow up period. Most of the children discharged in the second or third assessment had a normal hearing and impedance test. The group under review is of interest because it provides an overview of the natural history in a two year period of hearing impairment or flat impedance of untreated children. Approximately half of these children improved spontaneously between two successive assessments. The children sent to general practitioners had a lower rate of recovery as only six out of 23 had a normal impedance and eight out of 24 had normal hearing in the follow up assessment.

SPEECH THERAPY

Table 5 shows the distribution of referred children according to age and the number and severity of language problems. A large percentage of the referrals were of children under 3 years. Most assessed children were diagnosed as having a language problem (80%) and of these most had at least a moderate problem according to the speech therapist. Altogether 108 problems were detected in boys and 77 in girls. In table 6 the children are distributed according to the most severe language problem and the number of sessions the children attended speech therapy during the follow up period. Only 23 children had 11 or more sessions of speech therapy. The main reason for a low attendance rate (10 or fewer sessions) was low compliance. Improvement with treatment was observed in half the children who had problems. Unfortunately the data on outcome were based on speech therapists' subjective assessment as results of the Reynell test were rarely available.

Table 6 Distribution of children by most severe language problem and number of speech therapy sessions in follow up period (excluding first assessment) of those for whom treatment was planned

	No of sessions						Others*†	Total
	1–5*	6–10*	11–15	16–20	21–30	≥30		
Articulation:								
Severe	—	—	—	—	1	1	1	3
Moderate	1	2	3	1	1	—	3	11
Mild	1	—	—	—	—	—	—	1
Expression and comprehension:								
Severe	1	3	—	—	1	1	3	9
Moderate	2	4	4	3	—	1	15	29
Mild	2	3	—	1	—	1	—	7
Two problems of similar severity:								
Severe	1	1	—	—	—	2	1	5
Moderate	—	1	—	—	1	—	—	2
Mild	—	—	—	—	1	—	—	1
Total	8	14	7	5	5	6	23	68

*Ten children attended fewer than 10 sessions: because did not keep appointment (n=6), were transferred (n=1), went to a language unit (n=1), needed interpreter (n=1), or had assessment of specific needs (n=1).

†Immediately transferred, moved to another district, or non-compliance.

Discussion

At a time of great interest in medical audit[1 3] this paper highlights a number of organisational and clinical issues related to the provision of an integrated screening system to detect and manage preschool children with a possible vision, hearing, or language problem. From an organisational viewpoint helpful information was obtained with respect to attendance, children referred but not seen at the specialist clinic, and time waiting for initial assessment. From a clinical perspective data were available about rate of justified referrals, changes in diagnosis over time, treatment compliance, and discharge policies. Valuable information was available on spontaneous recovery of children who were under review during the period of observation.

In this paper parents' concern about their child's referral to the specialist service was not assessed directly. However, a measure of their concern would be given by the attendance at the clinics. In this study both initial non-attendance and non-attendance after having contacted the clinic were assessed. Poor attendance at the specialist service was a serious problem in speech therapy where 25·1% of the children did not attend after three appointments were sent to the parents. The rate of non-compliance in speech therapy cannot be explained by change of address or general apathy because the non-compliance rate was well above that of the other specialties. The high non-attendance rate anteceded any direct knowledge of the speech therapy service. The parents may perceive this service as more dispensable than the ophthalmology and audiology clinics. Clinical medical officers, general practitioners, and health visitors should be prepared to spend time explaining to parents the reason and potential benefits for the child being referred to speech therapy. The advice to parents should be very carefully worded because parents may believe that language delay is synonymous with mental retardation. An added difficulty for the practitioners is that some of these parents have poorly developed language themselves.

Non-compliance after having contacted the clinic was high in ophthalmology and speech therapy. In ophthalmology the majority of those who did not comply after initial assessment were normal, although a substantial number had pseudosquint or family history of squint. Among those who had at least two assessments a large percentage were diagnosed with a vision deficit. Low compliance in children followed up by the orthoptist has been reported previously.[4] In the group with only initial assessment parents may have felt sufficiently reassured with the results of this examination whereas the orthoptist or ophthalmologist may have wished to undertake a second check. In the second group parents may have decided to stop coming after a child was diagnosed with a defect but not given a treatment or given a treatment that the child found unpleasant. It is possible that many of these parents looked for a second opinion elsewhere.

In speech therapy there was no clear association between severity of findings at initial assessment and rate of non-attendance. Severity of problems were similar for those attending only the first assessment and those attending more assessments. However, most of those attending more than 10 sessions of speech therapy had a moderate or severe language problem. Possible reasons explaining the very large percentage of non-compliance after initial contact are the laborious nature of the specialty that demands weekly visits, the existence of two waiting lists, one for initial assessment and the other for treatment, and the high turnover of these therapists during the period of observation. A possible solution to the low compliance would be to arrange with parents an acceptable length of treatment time. This is an area that needs close monitoring because low compliance will reduce the potential benefit of speech therapy.

There were long delays between referral and initial assessment in the three specialties. At our first six months of assessment almost all the children referred to speech therapy and ophthalmology had been seen. In contrast, only half the children referred to audiology had been seen in the first six months. Despite this, audiology had the highest compliance rate after first assessment. This would indicate that parents were worried by the possibility of a hearing problem in their child.

The initial assessment of referred children indicated that a very large percentage of them had a problem necessitating diagnosis and management in terms of treatment and advice. A conductive defect and, rarely, a sensorineural problem was suspected in 60% of the children referred to audiology. The yield of problems in ophthalmology was only 20%, but for a further 31% a more specialised staff was required to exclude a squint. In speech therapy very few children were diagnosed as not having a language problem, but the assessments were not based on a widely used item derived test.

The very high detection rate for conductive problems was unexpected given the intermittent nature of the problem and the very long waiting time for an appointment in this specialty. All the information in this study indicates that a large percentage of the children had a persistent defect. This is illustrated by the high percentage of children referred to the ear, nose, and throat department who were operated on, the high percentage referred to the general practitioner for medical treatment who were eventually referred to the ear, nose, and throat department, and by the persistence of an impaired impedance and/or hearing loss in the large group under review. As complications, inconvenience, and cost of surgery are not negligible[5] it is appropriate to observe these children with middle ear effusion until the persistence of the problem is well documented. In this study children with apparently similar results in the hearing assessment were, in some cases, sent immediately to the ear, nose, and throat department, sometimes referred to the general practitioner, and others kept under review. The variety of approaches could be explained by differences in the history of the hearing disorder such as number of episodes, hearing infection, language delay, and duration of the disorder. It

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is clear that for the severe and persistent conductive defect lack of intervention will result in significant delay of language development.[6] However, the relation between milder forms of hearing impairment or unilateral impairment with language development remain unproved and therefore urgent surgery may not be warranted on those grounds.[5] After the study period the audiology clinic changed policy and children are no longer sent to the general practitioner for medical treatment. This new approach is supported by our results showing that very few children improved their audiology problems after attending the general practitioner.

The ophthalmology examination uncovered a large number of refractive problems. Many children with refractive problems also had squint and/or low visual acuity. The design of the study does not allow us to contribute to the discussion of the relation between refractive problems, squint, and amblyopia.[7] Many of the visual acuity problems were minimal: only nine children had a visual acuity defect in the initial assessment. A further 12 children had bilateral 6/9 vision and were not defined as having a problem. These children were not given treatment. The great majority of children with tested low acuity were older than 3 years at the time of screening. If this low acuity was associated with a refraction problem, glasses only or glasses and occlusion were prescribed. Approximately 75% of treated children had good compliance during the period of observation. With the small number of children with refraction problems and defective acuity it is not possible to contribute to the discussion as to whether screening at 3·5 years is dispensable or whether the condition deteriorates if treatment is not provided.[7]

The assessment of the work of speech therapy would indicate that a large number of children improved during the period of treatment. There are two caveats to this finding. Firstly, that no quantitative and objective assessments were available for most children in the initial and final assessment. Secondly, that it is difficult to distinguish in this group those children that have a below normal language standard, but who will catch up spontaneously, from those who will have a persistent language delay.[8] There are several reasons why the Reynell test may not be frequently used by the speech therapist. In the initial assessment the Reynell test may not be suitable because the child's attention span is insufficiently developed and many therapists feel that at either end of the assessment range the test is not satisfactory. In the post-treatment assessments parents may refuse further sessions, or appointments are not kept, and some patients are placed on review. Some may recover spontaneously in this period and fail to attend for the final assessment to confirm improvement.

This audit of vision, hearing, and language referrals identified the very large number of children with a sensory or language problem in an inner city area from whom detection, reassurance, close follow up, or treatment were required. A very large number of conductive hearing problems did not seem to recede spontaneously over time. From this perspective it is difficult to agree with a recommendation that parental awareness alone[1] would uncover the sizable level of appropriate referrals identified by the current formal clinical examination. We fear that the children of the less articulate and knowledgeable segment of the community will suffer as a consequence of such a policy. However, a number of organisational problems with implications for the efficiency of the service were identified. A particular pattern for speech therapy was the low compliance in terms of attendance at the specialist clinic. This may be due to parents placing a low value on this service, suggesting that rates of attendance may be increased through explaining more fully the aims and pattern of treatment to parents. There was also a considerable gap between initial assessment and an appointment for specialist audiology services that might be reduced through better waiting list management. Other findings raise questions requiring further research. For example in ophthalmology there appeared to be considerable variability in the treatment of squint which raises questions of the relative outcomes achieved. Similary, there are questions of the effectiveness of speech therapy.

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A special conditions register

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Abstract

A special conditions register (SCR) linked to the child health system's register of all children has been in use in West Sussex since 1977. This paper describes the aims, organisation, and use of the SCR and gives examples of the aggregated data that may be obtained. Of the 155 000 children aged 0–17 resident in West Sussex in 1990, 4·3% were included on the SCR. Altogether 45·7% of children on the SCR had physical conditions with mild or no disability and 17·2% had moderate educational problems. The prevalence of severe hearing loss as defined was 1·7 per 1000 aged 5–17. The prevalence of diabetes mellitus was 1·2 per 1000 children aged 0–17. Validation of the SCR for diabetes mellitus found 35/36 of the eligible children were correctly registered and no child was incorrectly included. The conflicting priorities for maintaining a register for the care of individual children, for service planning, and for epidemiological research are discussed.

Background

In 1976 the Court report emphasised the need for continued surveillance of children with handicap.[1] Six years later only 78% of health authorities in England and Wales had some form of handicap register, only 12% had a computerised register,[2] and West Sussex had the only computerised special conditions register (SCR) which was linked to the central child register. Since then many district health authorities have developed their own stand alone computerised SCRs[3] and integrated SCRs are being developed by two large groups of district health authorities[4] for their child health systems (G Coleman. Special needs registers, 1989; unpublished).

Although the names 'handicap register', 'special conditions register', and 'special needs register' are used by different district health authorities, most reported registers include all children with ongoing significant medical and developmental problems and share the common aim of ensuring their special needs are met.[2–7]

Aims, development, and organisation

The three aims of the West Sussex SCR are to improve the care of individual children by ensuring that all those with ongoing medical, developmental or learning problems are identified and followed up, to monitor, evaluate, and plan services, and to facilitate epidemiological research.

Computerisation of the child health system began in 1962 in West Sussex.[6] In 1971 the West Sussex County Council was commissioned by the Department of Health and Social Security to develop a system on the 'sun-satellite' model with a central file of the child population as the 'sun' surrounded by 'satellites' for immunisation and vaccination, early child health, school health, and special conditions (West Sussex Area Health Authority Community Health Branch. A computer assisted system for the school health service, 1972; unpublished). The SCR was set up in 1977 and special condition files were created for all children age 0–19 on the central file at that time who came within the definition.

There are three district health authorities in West Sussex: Chichester, Mid Downs, and Worthing. The community paediatrician for Chichester is responsible for maintaining the SCR for all three and for the accuracy, effectiveness, and confidentiality of the register. The district health authorities purchase computing services from the West Sussex County Council for the whole of the child health system. The system runs on an IBM 3090 mainframe computer using overnight batch processing.

Variables recorded and sources of information

A child's file on the child health system is initiated by the detailed birth notification used in West Sussex (table 1). The child's Guthrie test results, immunisation status, and results of scheduled screening throughout childhood are reported to the system by the laboratory, health visitor, general practitioner, clinical medical officer, school doctor, or school nurse. The SCR, being part of the child health system, need contain only information related to special conditions (table 2). At present up to 15 entries can be recorded for each child. As the SCR is intended to identify and classify the child, not to replace the clinical records, this has proved adequate to date even for children with multiple handicaps.

Child development teams and other health professionals such as peripatetic teachers of the deaf and educational psychologists send reports to the system. Copies are received of hospital outpatient letters, discharge summaries, letters from regional centres, and death registrations. Health visitors are required to notify the community paediatrician when a child with a significant medical or developmental problem moves into the district. Reports from health professionals other than doctors are confirmed

Table 1 Variables recorded in the child health system from the birth notification

- Mother's age and obstetric history, including exposure to risk factors (for example, smoking, *x* rays) and use of medication during pregnancy
- Perinatal details, including mode of delivery, birth weight and gestation, Apgar score, postnatal jaundice, convulsions, or respiratory distress
- Birth order
- Congenital malformations
- Family history of illness—for example, tuberculosis, Down's syndrome, haemophilia
- Socioeconomic group

Table 2 Variables recorded in the SCR

- Main functional disability: physical, developmental (<5 years), educational (≥5 years), sensory vision, sensory hearing, speech, psychological, multiple
- Disability severity: none or mild (not requiring special treatment or schooling, early stages of chronic disease—for example, Still's disease, cystic fibrosis, diabetes mellitus), moderate (needing treatment or special schooling—for example, moderate learning difficulties, developmental delay with developmental quotient <70), significant (needing special schooling or increased support), or severe
- Diagnosis by ICD9 and supplementary codes
- School or unit attended
- Use of aids—for example, wheelchair or hearing aid
- Year of statement of special educational need

by hospital reports or by information obtained directly from the child's general practitioner.

In addition to this constant unscheduled updating the SCR is routinely updated every year. Each health visitor receives a list of children under 5 years of age in her practice whose names are on the SCR, to check their entry, and to identify children who should be added to or removed from the list. For school age children a list is sent for checking to each school doctor and nurse. Updating continues until the child leaves school; this will be at age 19 for many children with special educational needs. At age 20 the child's file becomes an archive file. Although children who die, move away, or improve are removed from the SCR, their data remain retrievable in the system.

Validation for diabetes mellitus

The SCR was validated in May 1990 for prevalent cases of children with diabetes mellitus living in Chichester health district and born on or after 1 January 1973. As diabetic children are almost certain to be attending hospital, consultants should be able to provide an independent external set of cases for comparison.[8] All paediatricians and nurses receiving referrals from the district were asked to identify cases known to them.

Thirty one children with diabetes mellitus were identified, and 30 of these children had been accurately recorded on the SCR. The remaining child had previously been accurately recorded but the diagnosis of diabetes mellitus had been deleted in error when diabetes insipidus was also diagnosed at 15 years of age.

An additional five children with diabetes mellitus on the SCR were not identified by the paediatricians and nurses. Further inquiry established that all five were correctly registered. Four were over 15 and had been transferred to adult specialists, who had not been approached. The paediatrician of the remaining child did not respond.

In summary, 35 of 36 eligible children were correctly registered on the SCR and no children were incorrectly included.

Uses of the SCR

Whenever a child is seen in a scheduled consultation, the latest information from the SCR is included in the clinic record. Once a year, before confirming the SCR entries for their children, health visitors and school medical officers review each case from clinical records, by discussion with colleagues (for example teachers at special schools) or by medical examination where appropriate.

In addition, the flow of information to the SCR leads to opportunistic review of individual cases by the community paediatrician. The aim is to safeguard children against the risk of assuming all aspects of care will be covered in follow up at a regional referral centre or a local paediatric outpatients department.

The SCR is used to ensure the local authority education department has been notified by the age of 2 that a child may have special educational needs and in future it will be used to provide the social services department with the register of disabled children required under the Children Act 1989.[9]

Information for monitoring, evaluating, and planning services is sent on request and after approval by the community paediatrician to health, education, and other professionals. Recent examples include advisory teachers requesting the number of children with hearing aids, the number of visually impaired children in mainstream school, and the number of children under 5 with developmental problems who will need nursery places. Information has been provided for the Director of Public Health's Annual Report in each of the three districts.

For epidemiology, the SCR has been recently used to calculate the prevalence in West Sussex of severe sensorineural hearing loss, of severe visual defect, and of deaf-blind children. Current research includes the identification of secular change and risk factors in congenital heart disease and childhood malignancy and outcome in low birthweight babies.

Children on the SCR

In October 1990 there were 155 033 children born between 1 January 1973 and 31 December 1989, currently resident in West Sussex, and included on the child health system's register of all children. A total of 6594 children (4·2%) were included on the SCR (table 3). By severity code, 50·5% of children on the SCR had mild disability or none and 33·5% had moderate disability. By function code, 53·7% of children had physical conditions, and 21·0% were in the educational category used for children with learning difficulties aged 5 years and over. By both severity and function codes, 45·7% of children on the SCR had a physical condition resulting in mild disability or none, and 17·2% had a moderate educational problem. Severe hearing loss, an uncommon condition clearly

Table 3 Children aged 0–17 on the SCR by function and severity of disability (n=6594)

Function	*Severity*				*Total (%)*
	None or mild	*Moderate*	*Significant*	*Severe*	
Physical	3015	388	117	21	3541 (53·7)
Developmental	34	100	66	0	200 (3·0)
Educational	50	1132	104	99	1385 (21·0)
Vision	77	39	24	5	145 (2·2)
Hearing	91	199	36	49	375 (5·7)
Speech	51	325	75	0	451 (6·8)
Psychological	11	15	115	212	353 (5·4)
Multiple	0	8	30	106	144 (2·2)
Total (%)	3329 (50·5)	2206 (33·4)	567 (8·6)	492 (7·5)	6594 (100·0)

defined, and asthma, a common condition less well defined, are used as examples of simple aggregate data available from the SCR.

The SCR was interrogated in February 1990 for prevalent cases of severe deafness among children born from 1 January 1972 to 31 December 1984, by year of birth. There were 110 children with average hearing loss in the better ear of 50 dB or more and 82 children with multiple handicaps which included hearing loss (ICD code 389·0). The denominator of all children born in these years and currently on the child health system was 111 899, giving a prevalence of 1·7 per 1000 overall with no statistical evidence for a trend over time.

The criteria for including a child with asthma on the SCR are that (i) the child has had more than one hospital admission for asthma or requires regular courses of steroids and (ii) the child needs regular prophylaxis. In October 1990, 1211 children aged 0–17 met these criteria, or 18·4% of children on the SCR and 7·8 per 1000 children in West Sussex.

Discussion

Accuracy of population based registers of handicapped or impaired children has been found to increase with the number of sources of information, the amount of active reporting (where replies are requested whether or not there is a case to report), the length of the case finding period, and the age of preschool children. Conversely accuracy has been found to decrease with the number of variables recorded for each child, and most importantly with the mobility of the child population.[10–12]

The effect of mobility is to inflate a register, as it is more important for the care of the individual child to record movement in than movement out of the district.[10] As there is some evidence that handicapped children move more often than other children,[10 13] the effect of mobility is likely to overestimate the prevalence of handicap in a district health authority.

As the West Sussex SCR uses multiple sources and active reporting, and as mobility is low in the area, accuracy should be relatively high. The validation score of 35/36 for diabetes mellitus may be compared with a score of 57/68 reported in a similar validation of an SCR for diabetes mellitus elsewhere.[3] The West Sussex exercise is a reminder that for older children who have transferred to adult physicians paediatricians do not provide an independent external set of prevalent cases.

Although the SCR is updated until age 19 for children who remain in school, accuracy declines after age 16 when register entries for children who have left school are no longer reviewed each year by the school medical officer, and incident cases age 16–19 may never be added to the SCR. The accuracy of the child health system as the population denominator will also fall at school leaving age. For these reasons although the SCR continues to contribute to the care of some individual children until age 19, it is unlikely to contribute to service planning and research after age 16.

The proportion of the child population included on the SCR is a function of the level of morbidity and the level of ascertainment, but is primarily determined by the policy on criteria for inclusion, for example the policy on asthma. In West Sussex these factors lead to 4·3% of children being included on the register, but in Northumberland, with a different policy, the proportion is nearer 3%.[3]

The outstanding advantage of an SCR, which is linked to the population register of the child health system, is that all information is immediately available for each child. For analysis of aggregate data good computer programming is also needed. The quality of programming available to the West Sussex SCR has meant that to date it has been possible to meet all requests, and yet exploitation of the potential for monitoring, planning, and evaluating services, and for facilitating epidemiological research has only just begun.

Like the Community Health Index in Scotland[14] or the population register in British Columbia, Canada,[12] SCRs that form part of child population registers have considerable potential for identifying cases, controls, and risk factors for research, with appropriate safeguards for confidentiality and consent. The registers are population based and longitudinal and contain information for each child from birth with comparable information for other children from the same birth cohort, family, neighbourhood, school, treatment centre, and general practitioner.

As other studies have pointed out, however, there are problems in using a register for research which is maintained primarily for the care of individual children and for planning services.[2 10] Priorities may conflict in keeping the register up to date and coping with the problem of mobility. For the care of an individual child addition to the register is more important than deletion. For planning services the priority is an up to date list of resident prevalent cases and their future service requirements. For aetiology the priority may be an accurate list of all incident cases in the birth cohort and their history of exposure. Local and national priorities also conflict.

Studies of registers are unanimous in emphasising the need for comparability.[2 10 15 16] But effective coordination is lacking among and between the district health authorities currently developing SCRs, the social service departments currently setting up registers of disabled children, and the general practitioners currently computerising their practice registers (80% by

April 1991).[17] A national policy on health information systems for children with special needs is urgently needed. Without this the potential contribution to continuity of care for individual children, to planning and monitoring services at regional and national level, and to facilitating research in the aetiology and treatment of uncommon conditions will be lost.

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Chronic neutropenia

Experience in Texas (OG Jonsson and GR Buchanan, *American Journal of Diseases of Children* 1991; **145**: 232–5) confirms that chronic neutropenia in children is usually fairly benign. Fifty cases of chronic neutropenia (neutrophil count less than $1\cdot5\times10^9/l$ for more than eights weeks) were seen in a regional referral centre over a period of 13 years. Three children had congenital neutropenia and two siblings had cyclical neutropenia, one of whom died of staphylococcal septicaemia. Two other patients had severe disease, one of whom died of sepsis and the other was severely ill with massive lymphadenopathy, hepatosplenomegaly, and mouth ulcers but recovered after three years on treatment with cyclosporin.

The remaining 43 patients had a relatively benign course with frequent but usually mild infections of the upper respiratory tract, ears, and skin. Mild splenomegaly was noted in six and 80% of the children were younger than 2 years at the onset. Six of 23 girls had at some time an abscess or cellulitis involving the labia majora and in three the infecting organism was *Pseudomonas aeruginosa*.

Follow up information was available for 36 of the 43 children with benign disease. The white cell count had returned to normal in 23 of them after a median duration of 19 months. Thirteen were still neutropenic after a median interval of 18 months.

Chronic idiopathic neutropenia in childhood is uncommon. It usually runs a fairly benign course with mild infections responding well to antibiotic treatment and no need for antibiotic prophylaxis. Labial infection especially with pseudomonas may suggest this condition.

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Prognosis of motor development and joint hypermobility

E Tirosh, M Jaffe, R Marmur, Y Taub, Z Rosenberg

Abstract

In a study of 59 infants aged 18 months there were 20 with joint hypermobility and delayed motor development, 19 with joint hypermobility and normal motor development, and 20 normal controls. They were reassessed for motor function 3·5 years later at the age of 5 years. Both gross and fine motor performance were significantly delayed in the group of children who exhibited joint hypermobility and motor delay in infancy. No significant delay was evident in those with joint hypermobility only. Joint hypermobility resolved more frequently in children who presented normal motor development at age 18 months.

Infants with joint hypermobility and motor delay are a subgroup associated with a less favourable motor outcome and careful follow up is indicated.

The prevalence of joint hypermobility in infancy is about 17%.[1] Previous reports have indicated an association between joint hypermobility and early motor delay, even when no evidence for a neurological deficit is demonstrated.[1 2] It has been further suggested that this phenomenon is of a benign nature and that most infants with joint hypermobility will demonstrate a motor catch up by the age of 3 years.[2]

The aetiology of joint hypermobility, as well as the long term outcome of children with this entity, is unknown. Joint mobility can be determined by the structure of the joints and ligaments or by muscle tone.[3] Muscle tone in turn may be associated with various abnormalities, including those in the central nervous system such as mental retardation or cerebral palsy.[4] As fine motor function becomes increasingly sophisticated with age it was of particular interest to evaluate, in addition to gross motor achievement, the association between fine motor function and joint hypermobility in childhood.

The objective of the present study was twofold: (i) to assess prospectively the gross and fine motor proficiency of children who were identified as having joint hypermobility in infancy, either with or without motor delay, and (ii) to assess the association between joint hypermobility and motor function at the age of 5 years.

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Subjects and methods

Sixty children between the ages of 54 and 60 months (mean 57·3 months) with no known neurological, genetic, or cognitive problems, were evaluated. Each group of 20 children was randomly selected out of the following categories diagnosed at the age of 18 months: group A, joint hypermobility with gross motor delay (20 out of the original group of 35 children); group B, joint hypermobility with normal motor development (20 out of the original group of 25); and group C, normal joints and normal motor development (20 out of the originally diagnosed 90).

The criteria for joint hypermobility were as previously described.[1] After evaluation a skeletal deformity was found in one child in group B and he was excluded from the study. No significant differences in age ($p<0·3$), sex ($p<0·5$), or socioeconomic level ($p<0·4$) were found between the three groups. Mean (SD) age at enrolment in nursery school was comparable (24·8 (10·2) months) in the three groups ($p<0·14$).

PROCEDURE

All children were evaluated by an experienced paediatric physiotherapist, who had not participated in the previous stages of the study and was not aware of the child's original diagnostic category. Ninety per cent reliability and 96% reproducibility of the joint assessment had been previously established.[1] In addition, before the present evaluation, interobserver reliability of 1·0 for the joint evaluation and 0·9 for the gross motor measures was established among the examining physiotherapist, another physiotherapist, and a developmental paediatrician. No attempt was made to differentiate among the different mechanisms resulting in joint hypermobility.

MEASURES

Gross motor performance was evaluated with the Hoskins-Squires test for gross motor and reflex development.[5] The 14 items which pertained to the age range of 36 to 60 months were administered and coded as pass/fail. A child who failed to perform at least 50% of the items was coded as 'fail', and conversely a success rate of 50% or more was coded as 'pass'.

Fine motor development and visual motor integration were assessed with the following three tests: (i) block tower (from the Miller assessment for the preschool child[6]), (ii) the Bruininks-Oseretsky pegboard test,[7] and (iii) the Beery-Buktenica visual-motor integration test.[8]

A measure of parental perception of motor proficiency was derived from nine items of a questionnaire designed specifically for the study (table 1). The Conners' parent rating scale was administered in order to rule out the possible contribution of short attention span and/or hyperactivity to inadequate performance on the motor tests.[9]

One way analysis of variance and χ^2 tests were used for analysis as appropriate.

Results

The prevalence of gross motor dysfunction at age 5 years among the children of group A (joint hypermobility and motor delay in infancy) was significantly higher than in the other two groups ($\chi^2=19{\cdot}83$, $p<0{\cdot}003$) (table 2). No significant difference was found between groups B and C. Those children who demonstrated joint hypermobility and motor delay at age 18 months were significantly more likely to present the same association when they reached the age of 5 years ($\chi^2=6{\cdot}54$, $p<0{\cdot}01$) (table 2).

FINE MOTOR DEVELOPMENT AND VISUAL MOTOR INTEGRATION

Group A showed a significant disadvantage in the two fine motor tests. However, after Bonferoni correction, only the pegboard test remained significant. Forty five per cent of group A children failed the pegboard test, whereas only 21% of group B and 5% of group C children failed this test ($\chi^2=7{\cdot}2$, $p<0{\cdot}03$). No difference in the visual motor integration test was found between the groups.

PARENTAL PERCEPTION OF MOTOR PROFICIENCY

The parents of group A perceived their children as significantly less proficient in their motor abilities than did the parents of the other two groups. Group A scored a mean (SD) of 2·5 (1·8), group B 1·1 (1·6), and group C 0·7 (0·9) on the parent's questionnaire ($F=8{\cdot}0$, $p<0{\cdot}0008$).

No differences in perceived behaviour among the three groups were shown by the Conners' rating scale ($p<0{\cdot}83$).

Table 1 Child's motor proficiency: parental questionnaire

(1) Does your child play outdoors regularly with other children?	Yes	No
(2) Circle which of the following activities are enjoyed by your child: Swinging Playing in the sand box Sliding Ball games		
(3) Does your child prefer sitting in a push chair to walking?	Yes	No
(4) Does your child ask to be picked up excessively?	Yes	No
(5) Do you see your child as clumsy or with delayed motor development?	Yes	No
(6) Does your child trip or stumble a lot?	Yes	No
(7) Does your child bump into objects or people excessively?	Yes	No
(8) Does your child wash his hands and dry them independently?	Yes	No
(9) Which of the following articles of clothing can your child put on independently? Shirt Trousers Socks		

Discussion

The current prospective study is the first to provide data pertaining to motor ability outcome in children who presented with joint hypermobility in infancy. Previous reports addressed the associated gross motor patterns in infancy[1] and early childhood.[2] Those reports determined a gradual but complete resolution of the gross motor deficits. At the age of approximately 5 years it is possible to perform more sophisticated evaluations and thus diagnose more subtle dysfunction. It appears that 18 month old children with joint hypermobility and motor delay are at increased risk not only for gross motor, but also for fine motor problems in later childhood.

No statistical difference was found between the motor functions of children who were originally diagnosed as having joint hypermobility only and the normal controls. However, the former group scored consistently lower on the fine motor items.

At 5 years of age, the joint hypermobility of infants who had no motor delay at 18 months of age resolved more frequently (84%) than that of infants whose joint hypermobility was associated with motor delay (40%) (table 2).

The pathogenesis of this entity remains unknown. The fine motor findings at the age of 5 years suggest possible factors other than laxity of the ligaments and joint capsule or hypotonic muscle, as the fine motor function is not expected to be affected by these mechanisms. The course of this phenomenon varies, and infants with joint hypermobility but not motor delay at the age of 18 months seem to have a favourable outcome, whereas those with motor delay are at risk for both gross and fine motor problems in later childhood. It is therefore possible that there are two subsets of children with joint hypermobility, one group with normal motor development and no residual motor dysfunction and the other group with joint hypermobility and gross and fine motor dysfunction which may have its origin in the central nervous system. This subgroup might therefore benefit from a prolonged neurodevelopmental follow up. Whether their school performance will be affected remains to be investigated.

Table 2 Joint and development status of children at 18 months and 5 years of age. Figures are given as number (%)

18 Months (group)	*5 Years*				*Total*
	Joint hypermobility and motor delay	*Joint hypermobility only*	*Motor delay only*	*Normals*	
Joint hypermobility and motor delay (A)	8 (40)	4 (20)	5 (25)	3 (15)	20 (100)
Joint hypermobility only (B)	1 (5)	2 (11)	4 (21)	12 (63)	19 (100)
Normals (C)	1 (5)	1 (5)	3 (15)	15 (75)	20 (100)

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Sixty children between the ages of 54 and 60 months (mean 57·3 months) with no known neurological, genetic, or cognitive problems, were evaluated. Each group of 20 children was randomly selected out of the following categories diagnosed at the age of 18 months: group A, joint hypermobility with gross motor delay (20 out of the original group of 35 children); group B, joint hypermobility with normal motor development (20 out of the original group of 25); and group C, normal joints and normal motor development (20 out of the originally diagnosed 90).

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All children were evaluated by an experienced paediatric physiotherapist, who had not participated in the previous stages of the study and was not aware of the child's original diagnostic category. Ninety per cent reliability and 96% reproducibility of the joint assessment had been previously established.[1] In addition, before the present evaluation, interobserver reliability of 1·0 for the joint evaluation and 0·9 for the gross motor measures was established among the examining physiotherapist, another physiotherapist, and a developmental paediatrician. No attempt was made to differentiate among the different mechanisms resulting in joint hypermobility.

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A measure of parental perception of motor

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FINE MOTOR DEVELOPMENT AND VISUAL MOTOR INTEGRATION

Group A showed a significant disadvantage in the two fine motor tests. However, after Bonferoni correction, only the pegboard test remained significant. Forty five per cent of group A children failed the pegboard test, whereas only 21% of group B and 5% of group C children failed this test (χ^2=7·2, p<0·03). No difference in the visual motor integration test was found between the groups.

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At 5 years of age, the joint hypermobility of infants who had no motor delay at 18 months of age resolved more frequently (84%) than that of infants whose joint hypermobility was associated with motor delay (40%) (table 2).

The pathogenesis of this entity remains unknown. The fine motor findings at the age of 5 years suggest possible factors other than laxity of the ligaments and joint capsule or hypotonic muscle, as the fine motor function is not expected to be affected by these mechanisms. The course of this phenomenon varies, and infants with joint hypermobility but not motor delay at the age of 18 months seem to have a favourable outcome, whereas those with motor delay are at risk for both gross and fine motor problems in later childhood. It is therefore possible that there are two subsets of children with joint hypermobility, one group with normal motor development and no residual motor dysfunction and the other group with joint hypermobility and gross and fine motor dysfunction which may have its origin in the central nervous system. This subgroup might therefore benefit from a prolonged neurodevelopmental follow up. Whether their school performance will be affected remains to be investigated.

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	Joint hypermobility and motor delay	*Joint hypermobility only*	*Motor delay only*	*Normals*	
Joint hypermobility and motor delay (A)	8 (40)	4 (20)	5 (25)	3 (15)	20 (100)
Joint hypermobility only (B)	1 (5)	2 (11)	4 (21)	12 (63)	19 (100)
Normals (C)	1 (5)	1 (5)	3 (15)	15 (75)	20 (100)

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More about haemolytic uraemic syndromes

Regular readers of this journal will be familiar with recent British work on the clinical features, epidemiology, and microbiology of these syndromes (*Archives of Disease in Childhood* 1990:713–27) and the association with verocytotoxin producing *Escherichia coli*. A recent study from Buenos Aires has shown high rates of asymptomatic carriage in the parents and siblings of affected children.[1] Verocytotoxin was found in the stools of 39% (25 of 64) of household contacts though *E coli* 0157: H7, the villain of the piece in the British studies, was not grown. Of the 24 contacts from whom paired sera were collected 42% (10) showed seroconversion for neutralising antibody to verocytotoxin.

In Salt Lake City 61 patients were examined five to 18 years after an episode of haemolytic uraemic syndrome.[2] Nearly 40% (24) had proteinuria, reduced creatinine clearance, or both, and three of these 24 were also hypertensive. The abnormalities sometimes appeared after a period of apparent normality. These authors therefore recommend long term follow up of all patients after an episode of haemolytic uraemic syndrome even for mild cases apparently recovered.

This recommendation is supported by members of the nephrology team at the Children's Hospital, Birmingham.[3] They have shown that in children with a good outcome the urine ratio of protein to creatinine steadily declined over the first year to less than 20 mg/mmol in 87% of cases, whereas in those with a poor outcome the ratio invariably remained high.

Children who have apparently recovered from haemolytic uraemic syndrome should have a check on their blood pressure and an early morning urine protein:creatinine ratio from time to time throughout childhood and adolescence. Those with a high protein:creatinine ratio should be followed up more carefully. It is, of course, essential, if you haven't already done so, to persuade your laboratory to use a method capable of measuring low urine protein concentrations. The method used in Birmingham is the Coomassie blue dye binding technique.

ARCHIVIST

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Screening for undescended testes

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Abstract

There is general consensus among surgeons and paediatricians that cryptorchidism should be detected and treated by the age of 5 years, if not earlier. In reality, incomplete descent is often detected well beyond the age of 5. The effectiveness of local screening was assessed by reviewing the screening history and subsequent management of boys treated for undescended testes between 1983 and 1986. The detection rates for undescended testes in the boys under 5 years were low both for doctors and health visitors. In contrast, the school entry medical examination for 5 and 6 year olds had a higher screening yield. Over 40% of cases came to light as a result of parents recognising the condition and seeking medical opinion. Late detection had also occurred in some boys who had had previous genital surgery or examination. Methods to improve early detection and ways of monitoring proposed changes are discussed.

'Cryptorchidism is the only well established risk factor for testicular cancer'.[1] It is also associated with reduced fertility[2] and complications such as torsion.[3] [4] There is little evidence that early surgery improves fertility or reduces the risk of testicular cancer.[2] Nevertheless, because of the strong association between cryptorchidism and testicular cancer and the fact that changes in descended testes are easier to observe, there is general consensus among surgeons that cryptorchidism should be detected and treated by the age of 5 years,[5] if not earlier.[3] This view is endorsed by the report of the Joint Working Party on Child Health Surveillance, which states that 'infant boys should if possible be referred for surgical opinion before the age of 18 months'.[6]

Experience elsewhere has shown that in reality incomplete descent is often detected and referred well beyond the age of 5 years.[3] Our study was carried out in response to a similar observation by local surgeons that a number of boys with undescended testes were 'missed' by screening and referred for surgical assessment when they were considerably older than 5 years. The aim of the study was to assess the effectiveness of local screening for undescended testes.

Methods

We reviewed the screening history and subsequent management of all boys up to 15 years of age resident in north east Essex who were treated in the north east Thames region for undescended testes during the four year period 1983 to 1986. All hospital discharges with the diagnosis of undescended testes (ICD code 752·5) were identified by Hospital Activity Analysis. Hospital records, and community child health records if available, were examined for each case to ascertain the age at operation, source and pattern of referral to the general practitioner and surgeon, and any relevant medical history.

VALIDITY

Cases identified by Hospital Activity Analysis provided the best available estimate of true cases, because there is no other register of cases in the district. Only one girl and eight cases of torsion of the testes had been miscoded as undescended testes. It therefore seemed reasonable to assume that a similarly small number of true cases was probably lost to the study due to miscoding.

Boys who were screened outside the district were not included in the analyses. For example, boys who were born and had their check at 6 weeks of age outside the district were excluded from that part of the analysis. This exclusion was made for two reasons. Firstly, boys who moved into the district were not screened until the next formal screen was due (in this example, at the 8 month hearing check). Secondly, our aim was to report on the effectiveness of the local screening programme.

Results

In all, 313 operations on undescended testes were performed in the four year study period (table 1). All except one operation were performed in the district. Four operations were orchidectomies, the rest were orchidopexies. Nineteen boys had operations for undescended testes on two or more occasions during the study period.

AGE AT OPERATION (TABLE 1)

There was no child less than 1 year old. The boys divided into three roughly equal groups: those aged 1–4, those aged 5 and 6 (the age group most likely detected by school entry medical examination), and those over 6 years. The age distribution was consistent over the four year period.

Table 1 Age at operation

Age (years)	*No (%)*
1–4	92 (29)
5	52 (17)
6	57 (18)
7–15	112 (36)
Total	313 (100)

OUTCOME OF SCREENING BY DIFFERENT PROFESSIONAL GROUPS (TABLE 2)

In theory, all boys resident in north east Essex were examined by a doctor for testicular descent at birth and at the school entry examination at 5 years of age. The school medical examinations were always carried out by a clinical medical officer or senior clinical medical officer in child health. Neonatal examinations were carried out by a paediatrician or general practitioner depending on whether the baby was born in a consultant or general practitioner maternity unit.

In this district, basic development screening of children under 5 years was carried out entirely by health visitors during the study period, with clinical medical officers providing a second opinion when abnormalities were detected. Some general practitioners also carried out 6 week checks, but not as part of the district's child surveillance programme. Testicular examination was, however, excluded from the formal content of the health visitor's screening programme, and was only performed by a few health visitors at the checks at 6 weeks and 8 months at their own discretion.

Table 2 Outcome of screening in north east Essex district by different professional groups. Results are number (%) from notes available

Outcome	Screener*		
	Doctor	*Health visitor*	*Clinical medical officer*
Undescended testes noted:			
No follow up	23 (10)	14 (6)	10 (6)
Referral to general practitioner/surgeon	19 (9)	12 (6)	99 (62)
Descent noted	70 (32)	33 (15)	46 (29)
On waiting list for operation	—	—	3 (2)
Medical examination not done	—	—	1 (<1)
No record of testicular examination	108 (49)	158 (73)	
Operation already done	—	—	104
Notes not available	75	79	47
Total	295	296	310

*Boys were screened by a doctor as neonates or at 6 week check, by a health visitor at <5 years, and by the clinical medical officer at school at 5 or 6 years.

Data were analysed to determine the proportion of cases detected by each of these 'screener' groups (table 2).

Records were available for 220 boys screened by a doctor in infancy, for 217 boys screened by a health visitor at less than 5 years, and for 263 boys screened by a clinical medical officer at school. Detailed results are shown in table 2.

OUTCOME OF SCREENING UP TO SCHOOL ENTRY (TABLE 3)

The proportion of cases detected by each 'screener' group and treated by the age of 6 was analysed as a measure of the success of screening in the district (table 3). Doctors and health visitors had referred about 18% (17/92) and 9% (9/92), respectively, of cases operated by the age of 5 years. School doctors had referred 62% (68/109) of cases operated on between 5 and 6 years of age.

SOURCE OF FIRST REFERRAL (TABLE 4)

Looking at the detection and referral rates of 'screener' groups was useful to assess the success of each group in detecting cases. But some cases had been detected and referred by more than one person. For example, some boys referred by health visitors were already under surveillance by their general practitioner or paediatrician. We therefore recorded for each case the person responsible for initiating further management by making the first referral. Parents were responsible for nearly half of all first referrals (table 4). Just over a quarter of the operations were attributable to detection and referral by school doctors.

Table 3 Outcome of screening by age at operation (n=313)

Screener*	1–4 years		5–6 years		7–15 years (all operated too late)	
	Success†	*Failure†*	*Success†*	*Failure†*	*Success†*	*Failure†*
Doctor	17	40	2	31	0	22
Health visitor	9	19	1	10	2	18
Clinical medical officer	—	—	68	9	31	47

*Boys were screened by a doctor as neonates or at 6 week check, by a health visitor at <5 years, and by the clinical medical officer at school at 5 or 6 years.

†Success: noted and referred for action; failure: noted, no action taken, and noted as descended. Boys considered screening failures were detected and referred by others, for example, parents.

Table 4 Source of first referral by age

	Age (years)		
	1–4	*5–6*	*1–15 (all boys)*
No (%) referred to general practitioner:			
Parents	42 (46)	32 (29)	134 (43)
Health visitor	6 (7)	1 (1)	9 (3)
Clinical medical officer	1 (1)	57 (52)	82 (26)
Paediatrician	12 (13)	5 (5)	11 (4)
Self referral	—	—	2 (<1)
No (%) not referred to general practitioner:			
General practitioners own follow up	5 (5)	3 (3)	13 (4)
Surgeon's follow up	4 (4)	3 (3)	14 (4)
Paediatrician's follow up	—	—	8 (3)
Not known	22 (24)	8 (7)	40 (13)
Total	92 (100)	109 (100)	313 (100)

Table 5 Previous medical history (n=313)

	No (%)	*No whose management not influenced by history*
Previous orchidopexy same side	18 (5·8)	4
Previous orchidopexy opposite side	30 (9·6)	10
History of any other genital operation	29 (9·3)	22
Hospital admission	21 (6·8)	14
Any one of the above	67	37

MEDICAL HISTORY (TABLE 5)

We noted any past medical events that would have presented an opportunity for testicular examination (table 5). In all, 67 cases had histories of previous operations or hospital admissions, of which the detection or further management of undescended testes had not been influenced by such a history in 37 cases.

Discussion

This study has obvious limitations. It is not a population based study so we are unable to estimate the number of males in the general population with undescended testes who have still not been detected. Only those who have been detected and operated on are included in the present study because we were forced to rely on Hospital Activity Analysis files for the case finding. Nevertheless, the results have pointed the way to some practical measures to improve the effectiveness of screening. Secondly, the data reflects past screening practices. But screening policies had not undergone much change until recently, and the age distribution in 1989 of operations for undescended testes showed the same preponderance of boys older than 5 years.

The results showed low detection rates for undescended testes in those under 5. The obvious explanation for this is the omission of testicular screening from the formal content of the health visitors' programme.

Three additional reasons may have contributed to the poor results: (i) faulty or poor examination technique, (ii) confusion between maldescent and retractile testes; and (iii) no follow up of late initial descent between birth and 3 months. Late descent may sometimes progress to undescended testes by the first birthday.[6]

The difficulty in diagnosing maldescent must be recognised and probably accounts for many of the cases recorded as 'descended'. There is evidence that retractile testes are sometimes mistaken for undescended testes and vice versa.[7] The problem in distinguishing the two conditions is highlighted by the cases whose diagnosis was delayed despite previous genital surgery and expert surgical examination. It also reflects the need for good quality training in screening skills.

Another factor that may contribute to the confusion is the ascent of the testis from a previously normal to an undescended position. This unusual occurrence has been described by Atwell.[8] We support this hypothesis because we encountered 10 cases where descent had been recorded at two or more screening examinations by different people, which makes 'observer error' an unlikely explanation.

The school medical examination with its higher screening yield was a useful safety net to detect many more cases of maldescent before these boys escaped the developmental screening programme altogether. This finding supports the view that general practitioners should screen children at around 5 years of age, when school entry medical examinations are dropped or replaced by nurse health interviews. An additional benefit of this is that a standardised screening programme will be available to boys attending private schools who may not at present be receiving the district's school health service.

Over 40% of cases were diagnosed as a result of parents recognising maldescent and taking their sons to a doctor for examination. Parental participation is recognised as an important component of the recent recommendations on child health surveillance.[9] We suggest that late detection could be avoided if all parents of boys were taught by health visitors or general practitioners to be aware of the problem and encouraged to seek medical opinion when in doubt.

PROPOSED CHANGES

The new guidelines on child health surveillance[10] provide an ideal opportunity to resolve some of these problems. From April 1990, health authorities have had to specify clearly the content of their surveillance programme. We have proposed that general practitioners selected to carry out surveillance, and health visitors and clinical medical officers who are covering the rest of the population, should be given the responsibility to carry out a defined set of screening procedures including testicular screening. This should leave little scope for cases to be missed in the future.

All those who carry out screening should be given formal training so that they can examine testes correctly and communicate with parents to encourage their participation in surveillance.

PROPOSED AUDIT

Any changes we expect as a result of our recommendations need to be monitored, and we propose to do so in three ways. Firstly, surgeons will continue to notify us of older boys referred to them for the first time; this will enable us to review individual screening histories. Secondly, the age distribution of boys operated on for undescended testes will be reviewed annually for a five year period to determine whether the proportion of boys over the age of 5 years declines. Lastly, this study is to be repeated in five years' time to see whether the changes instigated have had the desired effect.

CONCLUSION

There had been considerable unease in the community child health department for sometime because of the omission of testicular screening from the health visitors' programme. However, the impetus to examine the problem came from the concern expressed by the surgeons. This study highlights the usefulness of audit, but the effort involved in collecting and analysing data pertaining to just one aspect of surveillance must not be underestimated. We are confident that simple measures such as greater health visitor involvement alone will substantially reduce late detection. Routine monitoring will show whether the primary objective of early detection is achieved in the future.

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Group A β haemolytic streptococcal disease

Beginning in the mid 1980s an increase in the incidence of rheumatic fever was reported from several centres in the United States and we braced ourselves for a resurgence of the disease in Britain, but so far it does not seem to have materialised to any great extent. Towards the end of the decade there were reports of an increase in invasive group A β haemolytic streptococcal disease in adults from various American centres and now a similar increase in children has been reported from North Carolina by Laurence Girner and his colleagues (*Journal of Pediatrics* 1991; **118**:341–6).

In three and a half years from July 1983 there were six cases at the Brenner Children's Hospital, Winston-Salem, and in the subsequent three and a half years there were 16 cases. The increase was not explained by changes in admission numbers, type of case, or diagnostic practice. Half of the 22 cases had no apparent underlying susceptibility to infection but of the remaining patients six had indwelling catheters, either vascular or peritoneal, and two were receiving immunosuppressive therapy. Sixteen children had septicaemia, two had peritonitis (one with an indwelling Tenckhoff catheter), and one each had orbital cellulitis, an infected ventriculoatrial shunt, a soft tissue abscess, and septic arthritis affecting a proximal interphalageal joint.

With group A streptococci continuing to cause problems in the United States we on this side of the Atlantic must clearly continue to be vigilant.

ARCHIVIST

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Multiple admissions under 2 years of age

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Abstract

Hospital admission rates before 2 years of age are reported for two complete birth cohorts born within a geographically defined area five years apart in 1980 and 1985. Admission rates for individual children in the cohort before 2 years of age showed an increase between 1980 and 1985 from 209 to 247 children/1000. The most significant increase took place in those children admitted three or more times (multiple admissions). Children admitted once only increased significantly but there was no significant change in the number of children admitted twice. A total of 2·3% of the total cohort in 1980 and 3·6% in 1985 were admitted three or more times and accounted for over 30% of all admissions. Age specific rates are reported for the 1985 cohort; 36% of those admitted had their first admission before 3 months of age and 76% before their first birthday.

The disproportionate contribution of children with multiple admissions to the admissions total renders admission data from Hospital Activities Analysis invalid unless linked to individual children. Cohort data based on a geographically defined population provide the most reliable admission rates and permit an accurate analysis of trends. The significance of and reasons for the upward trend in early childhood admissions are discussed.

An apparent increase in hospital admissions in childhood has been noted recently.[1–3] Various explanations have been advanced including a changing pattern of diagnosis and admission policy for childhood asthma,[4 5] the admission of children for primarily social reasons,[6] and the increased availability of children's beds resulting from shorter hospital stays.[1]

Hospital admission is disruptive to the family and expensive to the service. The emphasis in the Court report[7] and since[8] has been on child health services outside the hospital particularly the improvement of primary care for children. The apparent trend in admission of children to hospital suggests that hospital paediatric units continue to have a central role in the health care of children.

Hospital admission data are mainly derived from hospital activity data. These are of limited value as they do not relate to a definable child population and account only partially for those children admitted repeatedly.[2] Cohort data enable accurate rates to be calculated relevant to definable child populations and for different age groups. In addition children admitted frequently can be identified and their characteristics studied.

We report hospital admission rates in children under the age of 2 years for the whole population cohorts of Sheffield children born in 1980 and 1985. The trend in hospital admission for this age group is discussed.

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Methods

Details of all births at addresses within the Sheffield city boundary are routinely collected as part of the Sheffield Child Development Study (SCDS).[9] Daily contact is made with the three Sheffield paediatric units and admissions and admission diagnosis are recorded for all children under 2 years of age. No attempt is made to obtain admission details for those children leaving the Sheffield city area before the age of 2 or those living in Sheffield and admitted to hospital units outside the city.

The SCDS birth forms, onto which admission details are routinely entered, were examined for 6062 children born in 1980 (MAL) and 6179 born in 1985 (NJS). Children dying or moving out of the city before the age of 2 years were excluded from the study.

Admissions diagnoses, frequency of admission, and age at first admission were extracted for all children in the 1985 cohort; frequency of admission only was extracted for all children in the 1980 cohort.

Data were analysed to compare admission rates between the cohorts. Rates for all admissions, one admission only, two admissions, and three or more admissions (multiple admissions) were compared. Rates for all admissions by month of birth were calculated and compared between cohorts. Age specific admission rates were calculated for the 1985 cohort only. The χ^2 test was used to measure the significance of changes in admission rates between 1980 and 1985.

Results

Altogether 1269 Sheffield children born in 1980 and 1525 born in 1985 were admitted at least once before the age of 2 years. A total of 230 of the 1980 cohort were admitted twice in their first two years compared with 272 of the 1985 cohort; for multiple admissions (three or more) the respective figures were 142 and 221. Overall admission rates under 2 years and readmission rates for individual cohort children before 2 years of age are compared between cohorts in table 1.

There was a highly significant increase in the

Table 1 Comparison of overall admission rates of individual cohort children under 2 years of age for 1980 and 1985

	1980 cohort (n=6062)		*1985 cohort (n=6179)*		*p Value* (χ^2)
	No of admissions	*Rate/1000*	*No of admissions*	*Rate/1000*	
Total admissions of cohort children aged <2 years	1959	323	2483	402	<0·001
Children admitted once or more	1269	209	1525	247	<0·001
Children admitted once only	897	148	1032	167	<0·005
Children admitted twice only	230	39	272	44	0·10
Children admitted three or more times	142	23	221	36	<0·001

Table 2 Comparison between cohorts of number of admissions in multiple admission groups and those in groups with fewer than three admissions

	1980 cohort (n=1959)	*1985 cohort (n=2483)*
Group with multiple admissions	602	907
Group with fewer than three admissions	1357	1576

The difference between the two cohorts was significant: $p<0·001$.

overall admission rate and in the rate of admissions for individual cohort children between 1980 and 1985. The most significant change occurred in those children admitted three or more times. Those admitted only once showed a significant increase but not those admitted twice.

Of a total of 1959 admissions in the 1980 cohort, 602 (30·8%) were accounted for by the 2·3% of all cohort children admitted three or more times. For the 1985 cohort, 3·6% of children accounted for 36·5% of the 2483 admissions.

In both cohorts a small number of children contributed disproportionately to the total admissions. Table 2 shows an increase in the multiple admission group between 1980 and 1985 and a significant increase in their contribution to the total admissions.

Admission rates were calculated for each month of both cohorts. There was month by month variation in admission rates most noticeable in the 1980 cohort. No consistent pattern, however, was evident within or between cohorts and no significant differences emerged.

Altogether 548 children in the 1985 cohort were admitted before 3 months of age: 36% of those admitted and 8·9% of the whole cohort. A total of 813 children had their first admission before 6 months of age and 1171 before 1 year. Thus 77% of the children admitted had experienced their first hospital admission by their first birthday. Age specific admission rates/1000 for the 1985 cohort were 89 at <3 months of age, 132 at <6 months, 190 at <1 year, and 60 at 1–2 years.

Discussion

In a study, based on hospital activity data and the Oxford Record Linkage Study data, Hill reported an increase in hospital admissions between 1975 and 1985 of 88%.[1] The national cohort studies have shown an increase in admissions of children under 5 years of age: 18·5% in the 1946 cohort to 25·5% in the 1970 cohort.[10] A follow up study of the children of the 1946 cohort reported that 199·9/1000 second generation children were admitted at least once between ages 0–4 compared with 139·1/1000 first generation 1946 cohort children.[3]

Bax *et al*, from a study of two London inner city areas, found 18% of Camden children and 10% of Westminster children had been admitted at least once in the first year of life.[11] By 4·5 years more than a third of all children had been admitted at least once and 6% three or more times. While reported admission rates of 220/1000 for children under 2 years from cohorts in contrasting London boroughs derived from health visitor records.[12] From a retrospective study of Glasgow children under 11 months of age, using computerised discharge documents (SMR1), Gilchrist *et al* reported 19% of children experiencing at least one admission.[13] These results correlate well with the rates reported here.

The results of this study provide accurate recent admission rates for two cohorts of children under 2 years of age who were born five years apart in a geographically well defined area with a relatively stable population. We have shown a highly significant increase over the five year period in both the number of children admitted and the total number of admissions. The finding of 11% of children admitted before the age of 1 year from a comparable cohort of Sheffield children born between August 1975 and July 1976[14] suggest that the increase has been a continuous trend over at least 10 years. The sharpest increase was seen in the rate for children admitted three or more times rising by over 50% between the two cohorts. By 1985 almost a quarter of all children born that year in Sheffield had been admitted to hospital at least once. Though we have shown a noticeable month by month variation in admission rates, there is no discernible pattern over either year studied or between years.

In both cohorts, the small group of children having three or more admissions contributed almost a third of all the admissions and their contributions to total admissions increases significantly in 1985 compared with 1980. Hospital Activity Analysis data are unable to identify the multiple admission group and thus cannot accurately reflect admission rates and changes over time.

Our results suggest that, whatever the specific causes, changes in paediatric practice since the Court report,[7] with its emphasis on community based child health care, have failed to prevent large numbers of children being admitted to hospital. Hospital based practice continues to have a major role. This could be construed as a failure with negative consequences given the family and service problems associated with hospital admission or as resulting primarily from the increased availability of beds due to shorter lengths of stay.[1] Equally it could reflect changes in primary care and community child health services, which have produced a greater awareness of illness in infancy, improved liaison of primary and secondary services, and a consequent increased willingness to admit children.[15 16]

It is also possible that hospital admission is used as a means of temporarily removing children from home circumstances where social and family stresses are high. Further studies are necessary to clarify the causes of the upward trend in paediatric hospital admissions and to examine the characteristics of children experiencing multiple admissions.

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Gallstones

In a 10 year period (1979–89) 50 children and young adults aged less than 20 years were shown to have gallstones at the Children's Hospital of Buffalo, New York State (S Reif, DG Sloven, E Lebenthal, *American Journal of Diseases of Children* 1991; **145**: 105–8). There were 21 males and 29 females but boys outnumbered girls before puberty.

Eighteen patients had chronic haemolytic disease, eight had received parenteral nutrition, and seven developed gallstones during pregnancy. In 10 the gallstones were labelled idiopathic and the remaining seven had a wide variety of associated conditions.

Eight children were less than 6 years old at diagnosis, one of whom had the diagnosis made in utero by maternal ultrasound examination and four of the other seven had no symptoms of gallstones. The diagnosis was often made by ultrasound examination done for another reason such as urinary infection. As might be expected symptoms when present in younger children were less specific and pain was less well localised than at older ages. Four children had pancreatitis complicating their gallstones.

Thirty six patients underwent cholecystectomy but non-surgical management was preferred for gallstones after parenteral nutrition.

The authors do not discuss what to do about asymptomatic gallstones, a subject they describe as controversial.

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Antigliadin and antiendomysium antibody determination for coeliac disease

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Abstract

The value of IgG and IgA gliadin antibodies (AGA) was compared with that of IgA endomysium antibodies (EMA) for the diagnosis of coeliac disease. Three hundred and six of 340 (90%) children with untreated coeliac disease (flat mucosa) had EMA and 338/340 (99·4%) had IgG AGA and/or IgA AGA. Only 1/340 (a 7 year old boy with selective IgA deficiency) had neither AGA nor EMA. Absence of EMA is more frequent in coeliac patients younger than 2 years than in older patients (32/277 compared with 1/62). EMA were present in 4/211 (2%) of comparison subjects (normal mucosa), IgA AGA in 12/211 (6%), and IgG AGA in 74/211 (35%). The specificity of AGA cannot be calculated from these figures as they are biased. The combined determination of AGA and EMA, taking advantage of the high sensitivity of AGA and the high specificity of EMA, gives an excellent prediction of the condition of the mucosa: 247/248 patients (99·6%) with positive EMA and positive IgG AGA and IgA AGA had a flat mucosa, whereas 136/137 patients (99·3%) with neither AGA nor EMA had a normal mucosa.

During a gluten free diet EMA and AGA disappear. Their presence or absence is therefore an indicator of dietary compliance. After reintroduction of gluten into the diet 110/134 (82%) of the patients who had a flat mucosa at diagnosis relapsed, but 24/134 still had a normal mucosa after 2–15 years of challenge. All these patients without a morphological relapse were less than 2 years old at diagnosis so we conclude that patients who are young at diagnosis should be challenged. AGA often reappear earlier than EMA. After one month of challenge 93% of patients are AGA and 69% EMA positive. After more than three years of gluten intake the percentage of AGA positive patients decreased to about 50% whereas the percentage of EMA positive sera was then highest (93%). Therefore EMA are more sensitive for the detection of 'silent' relapse after prolonged periods of gluten intake.

It is well known that the formation of small amounts of antibodies to ingested proteins is a normal physiological occurrence. Low concentrations of antibodies to proteins in nutrients can therefore be demonstrated in nearly all subjects if the test method used is sensitive enough. This is also true for antibodies against gliadin (AGA).

In 1958 it was first shown by Berger in the Basel Children's Hospital that raised concentrations of antibodies to gliadin were associated with gluten enteropathy.[1] We subsequently tried to establish a simple and reliable test for measuring AGA in different immunoglobulin classes.[2] This test was expected to be useful for diagnostic purposes.[3–6] The aim was therefore to discriminate between patients with coeliac disease and patients with other malabsorptive disorders and not to detect the very low concentrations of antibody physiologically present in nearly all healthy individuals.

In the last few years several papers have appeared on the determination of antibodies against gliadin as a screening test for coeliac disease. Most authors agree that IgG antibody determinations are sensitive but not pathognomonic but IgA antibodies are more specific but less sensitive.[5 7–19]

In 1983 Chorzelski *et al* described IgG antibodies against endomysium (EMA) and found a close correlation between these antibodies and patients with dermatitis herpetiformis. Later they also found EMA in patients with coeliac disease.[20 21] EMA are directed against extracellular reticular fibres in the endomysium that surrounds the smooth muscle cells of many species.

Our aim was to compared the diagnostic significance of IgG AGA and IgA AGA with that of IgA EMA for coeliac disease in children.

Patients and methods

PATIENTS

We studied 551 patients who had undergone a first jejunal biopsy because of suspected coeliac disease from children's hospitals throughout Switzerland and Germany. Their ages ranged from 4 months to 18 years. All were under investigation for either gastrointestinal disease, failure to thrive, iron deficiency anaemia, short stature, or various malabsorptive disorders. Their sera were sent to the Laboratory for Microbiology and Immunology of the Children's Hospital in Basel for determination of AGA. At the beginning of the study the patients underwent biopsy without the results of the AGA determination being known. During the course of the study this procedure gradually changed as we came to clinical conclusions from the AGA results. For example, as a precaution patients who were positive for AGA were later biopsied even when the suspicion of coeliac disease was only slight. Therefore the percentage of false positive results increased during the study period. For an unknown number of patients who were negative for AGA we have no documentation regarding a jejunal biopsy. The influence of this selection on the statistical evaluation of AGA results is discussed later. The jejunal biopsies were performed and analysed in different hospitals in Switzerland and in Germany. At the time of blood sampling and jejunal biopsy all children were on a gliadin containing diet. A total of 340 children showed a flat mucosa (total or subtotal hyperplastic villous atrophy with hyperplasia of the crypts). In 211 with a normal mucosa or only partial villous atrophy coeliac disease could be excluded. These children were studied as a comparison group. Children with a flat mucosa in the small intestine after exclusion of cows' milk intolerance and viral diseases, and with regression of all symptoms in a few weeks after the introduction of a gluten free diet, were considered to have coeliac disease irrespective of whether their diagnosis had been confirmed by a biopsy after challenge.

For the following reasons we did not wait for all patients with coeliac disease to be biopsied three times. (1) Some centres of paediatric gastroenterology now refrain from challenging children with gluten. They accept that approximately 5% of originally well documented patients will not relapse after challenge. (2) The question of the incidence of transient coeliac disease is still unsettled and it remains uncertain whether the few patients who do not relapse after challenge are patients with transient coeliac disease or are incorrectly diagnosed.

The other patients who were entered in the study included 86 children who had multiple blood samples taken after varying periods on a gluten free diet. There were 135 children with morphological relapse after reintroduction of gliadin into their diet (110 with initial biopsy, 25 without initial biopsy). Twenty four children were included who did not have mucosal relapse after reintroduction of gliadin into their food, although their mucosa was flat on the initial biopsy specimen. Finally there were 10 patients without mucosal relapse after reintroduction of gliadin, without an initial biopsy.

At the time of the determinations for AGA the biopsy results were not known. Determinations for EMA were often performed retrospectively on the serum samples still available.

METHODS

The fluorescent immunosorbent test was used for the determination of AGA as described elsewhere.[2 3 5] EMA were determined as follows: unfixed cryostat sections of monkey oesophagus (Virimmun Diagnostika GmbH) were incubated with the patient's serum that had been diluted 1:10 in phosphate buffered saline. The antibiotics bound to the endomysium of the smooth muscle cells were made visible by overlaying the sections with a fluorescent anti-IgA serum in an appropriate dilution. Under the fluorescence microscope a brilliant green network was seen particularly in the lamina muscularis.

STATISTICAL ANALYSIS

As is clear from the description of the patients the data reported here are not the result of a planned investigation for which the hypotheses to be tested were stated in advance. Statistical analysis was therefore restricted to exploratory data analysis and confirmatory significance tests were applied only with great caution.

Sensitivity and specificity

Sensitivity is defined as the percentage of positive results in patients with the disease in question. Specificity is defined as the percentage of negative results in patients not suffering from the disease in question. In the case of AGA, estimates of sensitivity and specificity are biased by the fact that only a small proportion of the patients with negative AGA tests underwent biopsy.

Most sera sent to our laboratory have negative results for AGA. On the other hand a positive test for AGA was regarded as an indication for biopsy. The prevalence of false positive cases shown in table 1 was therefore higher than in the original population. In order to compensate for this bias a method proposed by Begg and Greenes was used.[22]

No such direct connection between the test result and the decision to perform a biopsy exists for EMA. Neither in children with a flat mucosa nor in those with a normal mucosa could a significant association between the tests for AGA and EMA be demonstrated (χ^2 test in 2×2 tables). Estimates of sensitivity and specificity can therefore be calculated from the present data without gross systematic errors. From a theoretical standpoint a planned experiment for the determination of sensitivity and specificity would be desirable. In order to obtain substantially more accurate estimates than in the present study, several hundred subjects with a flat mucosa as well as with a normal mucosa would be necessary. On ethical grounds such a procedure cannot be advocated.

Predictive values

The positive predictive value of a test is defined as the proportion of true positives in the total number of positives, and the negative predictive value of a test is defined as the proportion of true negatives in the total number of negatives. Both predictive values are related to the prevalence of the disease in the population studied and therefore are not characteristic constants of the test procedure. In the present data the positive predictive value of the case where all three antibody tests were positive was estimated as

Table 1 EMA correlated with AGA in children with untreated coeliac disease (flat mucosa). Results are number of EMA positive sera/total number (%)

IgA AGA	*IgG AGA*	*Age (years)*		*Total*
		0–2·0	*2·1–18*	
+	+	208/232 (90)	39/39 (100)	247/271 (91)
−	+	37/45 (82)	19/19 (100)	56/64 (88)
+	−	0	2/3 (67)	2/3 (67)
−	−	0	1/2*	1/2*
Total		245/277 (88)	61/63 (97)	306/340 (90)

*One patient with selective IgA deficiency.
+/−, positive/negative for antibody.

247/248=0·996 (see later in table 3). It may be argued that this estimate grossly exaggerates the true predictive value because of the above mentioned bias in the present data. This argument is not valid for the data were collected in such a way that false positive cases would probably have been detected. On the other hand the negative predictive value of the case where all three tests gave a negative result was estimated as 136/137=0·993. This value is probably too low as in a large number of negative cases the state of the mucosa was not examined.

Results

ANTIBODIES IN CHILDREN WITH UNTREATED COELIAC DISEASE AND CONTROLS

The different combinations of results for IgG AGA and IgA AGA were correlated with the results for EMA in 551 children who had a jejunal biopsy. Of 340 patients with untreated coeliac disease (flat mucosa), 306/340 (90%) had EMA, 335/340 (99%) were positive for IgG AGA, and 274/340 (81%) were positive for IgA AGA (table 1). The prevalence of EMA was roughly the same in patients with and without IgA AGA. Only one of the two coeliac children ever found to have no AGA produced EMA. The other was a patient with a selective total IgA deficiency who therefore could not produce either IgA EMA or IgA AGA. Two of the three children with only IgA AGA, a very rare situation which has so far been found only in adolescents, also had EMA.

Absence of IgA EMA is more frequent in patients younger than 2 years than in older subjects (32/277 compared with 1/62, the patient with IgA deficiency is omitted from the statistical analysis). This difference is significant: p=0·0082, Fisher's one tailed exact test in 2×2 tables.

We found EMA in only 4/211 disease controls (table 2). Altogether 207/211 (98%) of the patients with a normal mucosa or only partial villous atrophy were negative for EMA. Twelve of 211 (6%) had IgA AGA and 74/211 (35%) IgG AGA. The estimated sensitivity of the EMA test is 90% and its estimated specificity is 98%. The sensitivity and specificity of AGA cannot be evaluated from the presented figures as they have a statistical bias (compare selection of patients and statistical discussion). In former papers the sensitivity was calculated to be at least 96% and the specificity 97%.

Table 2 EMA correlated with AGA in disease controls (normal mucosa or partial villous atrophy). Results are number of EMA positive sera/total number (%)

IgA AGA	*IgG AGA*	*Age (years)*		*Total*
		0–2·0	*2·1–18*	
+	+	1/8 (13)	0/4 (0)	1/12 (8)
–	+	1/40 (3)	1/22 (5)	2/62 (3)
+	–	0	0	0
–	–	0/75 (0)	1/62 (2)	1/137 (1)
Total		2/123 (2)	2/88 (2)	4/211 (2)

+/–, positive/negative for antibody.

If we summarise the results of determinations of AGA and EMA and distinguish between patients with three, two, or only one positive antibody test (table 3), it is obvious that the combined determination of these antibodies gives an excellent prediction of the condition of the mucosa, particularly in patients with three concordant antibody results. It takes advantage of the very high sensitivity of AGA determination and the very high specificity of EMA determinations. Of the 248 patients with three positive tests, namely positive EMA and positive IgA AGA as well as IgG AGA, 247 (99·6%) had a flat mucosa and were therefore serologically correctly diagnosed as having coeliac disease. Only one showed a normal mucosa. The percentages of patients with a flat mucosa decreased if only two or one tests were positive. Altogether 136 out of 137 (99·3%) patients with neither AGA or EMA had a normal mucosa and were also serologically correctly diagnosed as not having coeliac disease. Conversely the percentage of patients with a normal mucosa decreases if one, two, or even three tests are positive. Of a total of 551 biopsied patients with AGA and EMA determinations, 385 (70%) had three concordant antibody results. One hundred and sixty six (30%) of the 551 patients did not have concordant antibody results, which means that the condition of the mucosa cannot be predicted with the same certainty. Nevertheless, the frequency of a flat mucosa is very high if the test for EMA is positive, even with a negative test for IgA AGA.

ANTIBODIES IN CHILDREN ON A GLUTEN FREE DIET

AGA like EMA disappear on a gluten free diet. IgA AGA disappear very quickly in two to six months so that they are useful as a diet control.[5] By contrast IgG AGA need a long time, sometimes more than a year, to become negative. EMA persist longer than IgA AGA but not as long as IgG AGA. Figure 1 shows the percentages of sera that are still positive in 86 patients

Table 3 Predictive values of different test results from 551 patients

Antibody test			*No of cases with:*		*Predictive value (%)*	
EMA	*IgG AGA*	*IgA AGA*	*Flat mucosa*	*Normal mucosa*	*Positive*	*Negative*
+	+	+	247	1	99·6	—
+	+	–	56	2	96·6	—
+	–	+	2	0	—	—
+	–	–	1	1	—	—
–	+	+	24	11	68·6	31·4
–	+	–	8	60	11·8	88·2
–	–	+	1	0	—	—
–	–	–	1	136	—	99·3

+/–, positive/negative for antibody.

who had multiple blood samples taken after increasing periods on a gluten free diet.

REINTRODUCTION OF GLUTEN INTO THE DIET

(a) Clinical results

To demonstrate the persistence of gluten intolerance gluten is often reintroduced into the diet of patients with coeliac disease. In our study a total of 169 patients were challenged and rebiopsied after varying periods on gluten containing food (table 4). In 35 of them coeliac disease was initially diagnosed purely on the basis of the clinical symptoms with neither an initial biopsy nor antibody determinations. Twenty five (71%) of these 35 patients showed a pathological mucosa after challenge. Ten children had no mucosal relapse after at least two years of challenge. They were probably never affected by coeliac disease. On the other hand 134/169 patients were initially diagnosed with a jejunal biopsy showing a flat mucosa. Altogether 110 (82%) of 134 children relapsed after varying periods of challenge, but 24 (18%) showed a normal mucosa after at least two years of challenge. It must be assumed, however, that some of these patients could relapse later on because their challenge period before biopsy was still too short to definitely exclude persistent gluten intolerance. Thus 9/134 (7%) had undergone challenge for a period of two to four years, but 15/134 (11%) still showed a normal mucosa even after four to 15 years of regular gluten intake, although their mucosa was flat at the initial biopsy (table 4).

The children with relapse were initially diagnosed at an age between 5 months and 10·9 years (median 1·3 years). All children without relapse were younger than two years at diagnosis (6 months–1·7 years, median: 10 months).

The age at challenge varied widely from just under 3 to 18 years in patients both with and without relapse. The final morphological outcome therefore does not seem to be influenced by the age at challenge.

Persistent gluten intolerance was definitively demonstrated in 110 patients who had been biopsied at diagnosis. Some of them had to be biopsied two or even three times during challenge before the relapse became morphologically manifest, which results in 125 biopsies being carried out in 110 patients. Twelve (28%) of 43 patients who were biopsied after one month of challenge still had a normal mucosa. If the biopsy was postponed until between two months and one year of gliadin loading, only 2/33 (6%) did not yet show a morphological relapse (their challenge period was seven or 10 months), and only 1/19 (5%) if it was postponed from one to two years (challenge period 20 months). All biopsies done after at least two years of challenge were pathological.

(b) Antibodies during challenge

AGA titres after challenge in patients with relapse were often not as high as the original titres in untreated coeliac disease. In about 50% of sera only IgG AGA were found and in a few cases only IgA AGA. We therefore can discuss only AGA irrespective of the isotypes found. Before challenge the percentage of antibody positive patients (fig 2) was low (AGA 23%, EMA 13%) but not zero; this is a reflection of dietary non-compliance. AGA are generally produced shortly after the beginning of the challenge, as shown in fig 2. Fifty (93%) of 54 patients with antibody tests produced AGA after 14 to 35 days. The percentage of sera with AGA is highest (97%) after a challenge period of about four weeks to three months and decreases thereafter to only 49% after three or more years of gliadin intake. As regards individual patients, some of them showed the following antibody time course. The AGA increased in an initial phase but later declined again and in some patients even became negative, although the biopsy specimen showed a severely damaged mucosa at the end of the challenge. This increase and decrease of AGA in individual patients explains the diminishing percentages of patients positive for AGA during long challenge periods (fig 2). EMA are produced later in the challenge than AGA but they do not disappear after a prolonged challenge (fig 2). In the first month of challenge only 69% of patients had EMA. The highest percentage (93%) of patients positive for EMA was reached after three and more years of gliadin intake.

AGA were found in 9/54 patients (16%) without morphological relapse and EMA were present in 6/54 (11%). These antibody positive patients were challenged for between three months and four years. Some of them, espe-

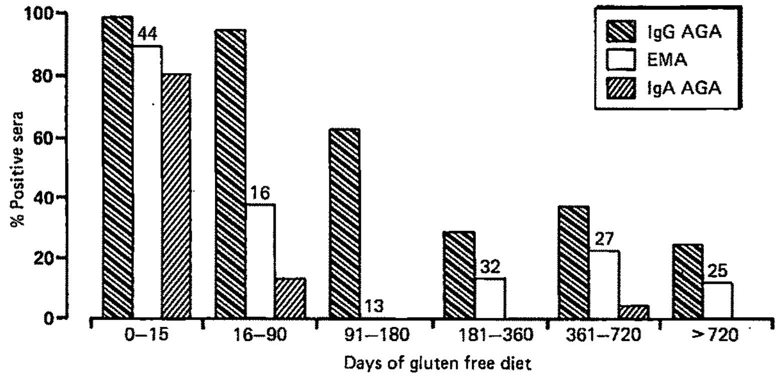
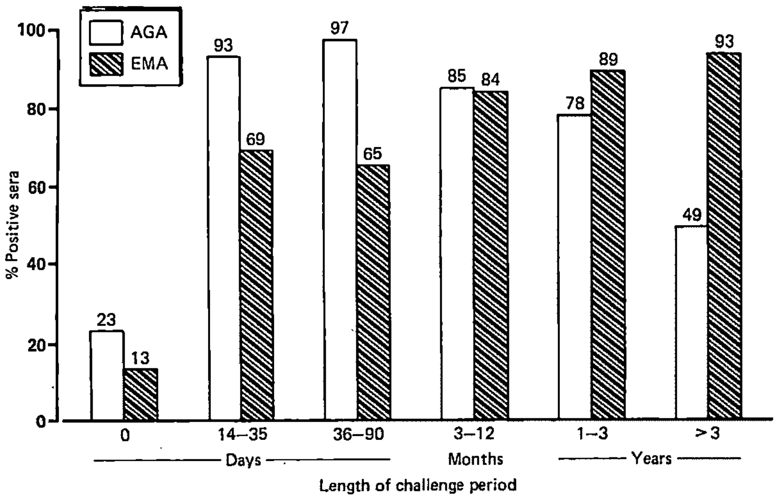


Figure 1 Frequency of IgA AGA, IgG AGA, and EMA after introduction of a gluten free diet (157 sera from 86 children; number of sera in each group is shown).

Table 4 Clinical results of 169 rebiopsied patients after challenge with gliadin containing food. Results are number (%)

	Patients with relapse: mucosa pathological after challenge	*Patients without relapse: mucosa still normal after challenge period from*	
		2–4 Years	*4–15 Years*
Patients without initial biopsy (n=35)	25 (71)	6 (17)	4 (11)
Patients with a flat mucosa at initial biopsy (n=134)	110 (82)	9 (7)	15 (11)



AGA	23/100	50/54	28/29	73/86	67/86	17/35
EMA	10/75	25/36	13/20	49/58	55/62	27/29

Figure 2 AGA and EMA before and during challenge with gluten in patients with relapse (390 sera from 135 children; percentage of positive sera in each group is shown; number of positive sera/total number tested is shown below figure).

Table 5 The condition of the mucosa correlated with antibodies at the time of biopsy during challenge. Results are number of antibody positive sera/total number tested.

	Length of challenge			
	1 Month	*2–12 Months*	*1–2 Years*	*>2 Years*
Flat mucosa	37/38	36/38	22/22	36/37
Normal mucosa	5/12	1/2	0/1	0/0

There were 150 biopsies and blood samples from 135 patients with final relapse.

cially those with EMA, are expected to relapse later.

(c) The value of antibodies in indicating the appropriate time for jejunal biopsy during challenge
One hundred and fifty biopsy findings from the 135 patients with final relapse (110 with and 25 without biopsy at diagnosis) were correlated with the respective antibody results at the time of biopsy (table 5). All patients except four had antibodies (either AGA or EMA or both) at the time of biopsy if the mucosa was pathological. One patient was negative after one month, two after two to 12 months, and one after more than two years of challenge, although the mucosa was pathological at the time. Six of 15 patients whose mucosa was still normal at the first biopsy during challenge were already antibody positive. It may be concluded that nearly all patients with a relapse produced antibody but that it sometimes appears before the mucosa becomes pathological.

Discussion

AGA were first described in 1958.[1] Since then much has been done to improve antibody determination techniques. Two methods in particular have been widely used and thoroughly proved: the fluorescent immunosorbent test and the enzyme linked immunoabsorbent assay (ELISA). The results of both assays are comparable and have been extensively reviewed.[18 23] It is now generally accepted that IgG antibody determinations are sensitive but not pathognomonic for coeliac disease whereas IgA antibody determinations are much more specific but less sensitive.[5 18 19] As coeliac disease is 10-15 times more frequent in people with selective IgA deficiency than in those with normal IgA it is not advisable to omit IgG antibody determinations, although IgA antibodies are more specific.[24]

In the last few years an additional test for EMA has been introduced and shown to be highly specific for coeliac disease.[20 21 25–28] Our aim was to compare AGA with EMA for diagnostic purposes. In an earlier study we examined AGA in untreated coeliac disease and in disease controls and obtained a sensitivity of at least 96% and a specificity of 97% for combined IgG AGA and IgA AGA determinations.[5] In the present study 35% of children with a normal mucosa had IgG AGA, mostly in very low titres, and 6% had IgA AGA. It is not possible to calculate the specificity of AGA from these figures as they have a statistical bias (see earlier). EMA, however, have an estimated sensitivity of 90%. Thirty four of 340 children (10%) with untreated coeliac disease had no EMA. All except two of them were younger than 2 years at diagnosis. This shows that the sensitivity of EMA is age dependent (80% in children <2 years, 97% in children >2 years). It may be speculated that some of the patients without EMA might have produced EMA at a later age. Substance is lent to this conjecture by the development of EMA during challenge, where the relative frequency of cases positive for EMA increases with the duration of challenge with gluten.

The specificity of EMA was very high at 98% (207/211). The combined determination of AGA and EMA, taking advantage of the high sensitivity of AGA and the high specificity of EMA, obviously gives an excellent prediction of the condition of the mucosa (table 3). Particularly in those patients with three concordant antibody tests (IgG AGA, IgA AGA, EMA either all tests positive or all tests negative) the chance of an incorrect prediction is extremely small. For example, only one out of 248 patients (0·4%) with three positive antibody tests had a normal mucosa, whereas only one out of 137 patients (0·7%) with three negative tests had a pathological mucosa.

As a consequence of many studies[5–19] it has recently become the custom of many paediatric gastroenterologists not to take biopsy specimens from patients when no antibody can be found[29] unless a strong clinical suspicion of coeliac disease is contradictory to the serological result. A positive antibody result, however, is taken as an indication for biopsy. The question arises of whether it would not also be possible to refrain from carrying out a biopsy in children younger than 2 years if the three antibody tests (IgG AGA, IgA AGA, EMA) are positive. In this age group the number of children without relapse on challenge is very high, 11–18% in our study, even if these patients presented a flat mucosa at initial biopsy. A challenge after remission is therefore required in all cases if the children are less than 2 years old at diagnosis.

Only a challenge followed by biopsy will save many children (5–18%) with transient coeliac disease from having unnecessarily to follow a lifelong gluten free diet. Therefore the biopsy for diagnosing coeliac disease would not be eliminated but only postponed. This proposal for one biopsy at the end of the diagnostic procedure instead of one at the beginning in children younger than 2 years with three positive antibody tests is contrary to the revised criteria for diagnosis of coeliac disease,[30] which demand an initial biopsy for correct diagnosis in any case.

Nevertheless with a view to the future this possibility should be included in the general discussions of European paediatric gastroenterologists.

AGA and EMA decline on a gluten free diet, as has already been shown by other authors,[31] and may therefore be used as an indication of dietary compliance.

After reintroduction of gluten into the food most patients with coeliac disease relapse. But the question of the incidence of transient coeliac disease is still unsettled.[32] It is evident from our figures that a flat mucosa in young children does not constitute proof of lifelong coeliac disease. Persistent gluten intolerance was demonstrated in 82% of patients with a flat mucosa at diagnosis. Some of them had to be biopsied several times before the relapse was morphologically evident. Thus 12 out of 43 patients (28%) who had been biopsied after one month of challenge did not yet show any signs of relapse. In most patients the morphological relapse becomes evident after three to 10 months of challenge. All biopsies done after at least two years of gluten intake were pathological.

After reintroduction of gluten containing food, not only AGA[31] but also EMA are produced again. In many patients AGA appear earlier than EMA so that after a short period of challenge the percentage of patients positive for AGA (93%) is higher than the percentage of those positive for EMA (69%). The percentage of sera positive for AGA is highest after a challenge period of about one to three months (97%), but after prolonged periods of gluten intake it decreases to only about 50%. This decline in the number of patients positive for AGA after long periods of challenge reflects the titres for AGA in individual patients, where an initial increase and later on a decrease or sometimes even a negative titre may be observed although the mucosa is damaged at the end of challenge. By contrast the percentage of sera positive for EMA is highest (93%) after one or more years on normal food and stays at the level even after very long periods of gluten intake. Therefore EMA are more sensitive for the detection of a 'silent' relapse after prolonged periods of gluten intake.

In conclusion, nearly all patients with persistent gluten intolerance produce antibodies at some time, but they show a wide individual variation as regards time and the type (AGA, EMA) and quantitites of the antibodies they produce. The pathophysiological role of AGA and EMA is still unknown. As we showed recently,[33] EMA is probably identical with an antijejunal antibody directed against collagen fibres in human jejunum. We consider this antibody to be an autoantibody of coeliac disease.

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Uniparental disomy and genomic imprinting

Sex is dead. Oh, really? Yes, well it must be because, according to a distinguished group of geneticists,[1] it has left a legacy—the fact that chromosomes and genes come in pairs. Be that as it may, the phenomenon of genomic imprinting (see Archivist 1991:80) is a fascinating one which seems as yet to have no very satisfactory explanation. The most commonly quoted clinical example of this phenomenon is, of course, the fact that Angelman's syndrome and the Prader-Willi syndrome appear to result from a deletion in the same region of the long arm of chromosome 15 (15q 11–13) and the deletion is always of maternally derived material in Angelman's syndrome and of paternally derived in the Prader-Willi syndrome.

It was reported in 1989 that the Prader-Willi syndrome could result from uniparental maternal disomy—that is, both chromosomes coming from the mother.[2] Now two of a total of 76 patients with Angelman's syndrome have been shown to be disomic for the paternal chromosome 15.[1] As the patients are in all respects similar to others with this syndrome it seems unlikely that the absence of other maternally derived genes on this chromosome has any appreciable deleterious effect. Thus imprinting is clinically relevant in probably only a small proportion of the genome. It is not yet established that the responsible gene is the same in the two syndromes but if not identical they are very close or overlapping.

From the point of view of genetic counselling the finding is of some significance. When parental chromosomes are normal the risk of recurrence is low for Prader-Willi syndrome but higher (more than 8%) for Angelman's syndrome. If parental disomy can be demonstrated, however, that indicates a very low risk in either syndrome.

ARCHIVIST

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Nebulised water as a bronchoconstricting challenge in infancy

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Abstract

The pulmonary response to inhalation challenge with nebulised distilled water was measured in 100 sedated infants with a history of wheeze. Lung function was measured by total body plethysmography. Satisfactory results were obtained in 88 infants. Fifty one were considered to have responded by developing a greater than 20% decrease in specific conductance (sGaw) after nebulised water. Thirty two of these infants had previously been challenged with nebulised saline before but only one showed a greater than 20% decrease in sGaw after saline.

Twenty infants who developed signs of bronchoconstriction after challenge with nebulised water were rechallenged 20 minutes later. After the initial challenge a fall in sGaw of greater than 20% was found in 19 of the 20. After a second challenge with nebulised water only 15 (75%) showed a 20% or greater decrease in sGaw. Nine of the 20 infants remained sedated and were rechallenged for a third time. Eight showed a greater than 20% decrease in sGaw.

This study indicates that approximately 60% of infants with a history of wheeze will bronchoconstrict in response to inhaled nebulised water and that up to 75% show no evidence of a subsequent refractory period to inhaled water challenge.

Lower respiratory tract illness, such as bronchiolitis[1] and chlamydial pneumonia,[2] are associated with high prevalence rates of bronchial hyper-reactivity in future years. Understanding the airway response to pulmonary insults in the first year of life may help to determine the pathogenesis of reactive airways disease. Studies on the effect of antiasthma drugs on airway reactivity provide information on mechanisms occurring in asthma and are helpful in the assessment of new techniques. Histamine,[3] methacholine,[4] and cold dry air[5] challenges all produce bronchoconstriction in infancy. Nebulised water has previously been shown to be an effective bronchoprovocative agent in asthmatic adults[6] and older children.[7]

To study the effects of antiasthma drugs we planned to give infants nebulised water as a bronchoconstricting challenge, administer either a β_2 agonist[8] or sodium cromoglycate, and rechallenge with nebulised water. It was necessary to determine first whether any lack of response to the second nebulised water challenge was due to the drug exerting a protective effect or due to a refractory period after the initial challenge.

The aim of this study therefore was to determine the effect of repeated challenges with nebulised water on infants with a history of recurrent wheezing. The 20 infants in this study were chosen from 100 infants challenged with nebulised water. To illustrate how the 20 infants were chosen the results of all 100 patients are discussed briefly.

Methods

All patients had had at least two episodes of wheeze in the preceeding two months. All but nine of the patients had been seen during an episode of wheeze by one of the authors.

Once sedated with chloral hydrate (120 mg/kg) each infant was placed in the total body plethysmograph and allowed to settle for several minutes. Baseline lung function (thoracic gas volume and airway resistance) was then measured.

Thirty two of the infants were given ultrasonically nebulised saline (0·9%) from an intersurgical Variosonic nebuliser (21°C, volume fill 150 ml, setting 3, via an airtight latex mask for two minutes at a flow rate of 5 l/minute). After nebulisation, readings were taken for calculation of thoracic gas volume and airway resistance at regular intervals (every 2–3 minutes) until readings were back to a stable baseline. Results were determined as back to baseline when there was minimal changes (less than 0·5°) in the slope of the box pressure/slope readings from the face of the oscilloscope over a 5–6 minute period.

One hundred infants were then given ultrasonically nebulised water from the same nebuliser (21°C, volume fill 150 ml, setting 3) for two minutes. Again readings were taken for thoracic gas volume and airway resistance at 2–3 minute intervals until readings had become stable.

Twenty of these patients were selected for repeated water challenge when the pressure/flow slope on the face of the oscilloscope changed after the initial nebulised water challenge and was judged by the observer to indicate increased airway resistance. The 20 infants (13 boys and seven girls) studied had a mean (SD) age of 9 (3) months and had suffered from at least two episodes of wheeze in the preceeding months. The mean (SD) weight of the group was 9·1 (1·2) kg.

The 20 infants selected were rechallenged with nebulised water 20 minutes after the first

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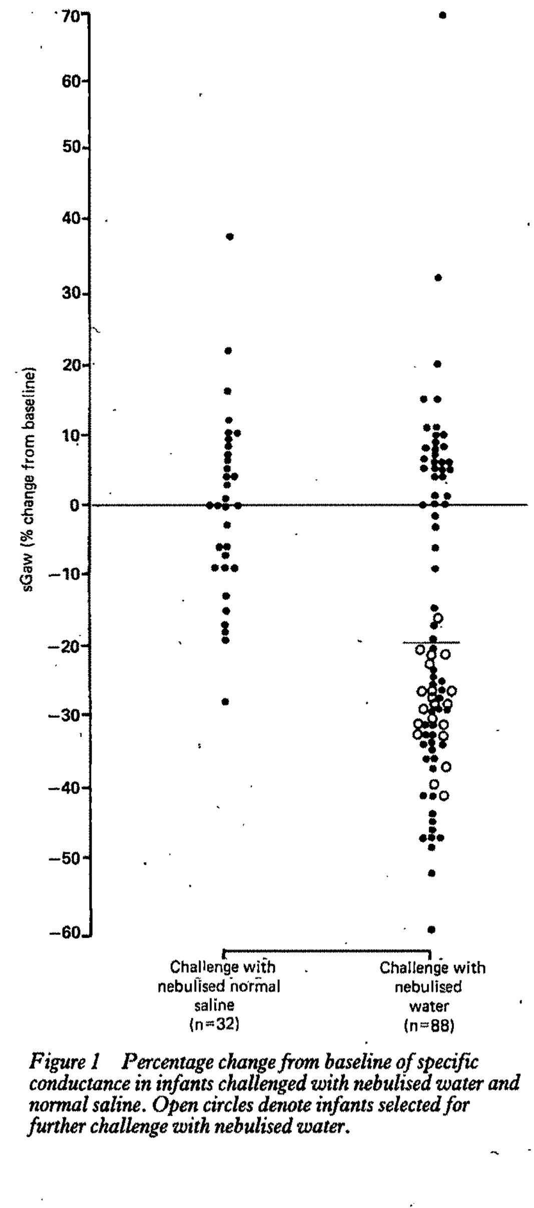

Figure 1 Percentage change from baseline of specific conductance in infants challenged with nebulised water and normal saline. Open circles denote infants selected for further challenge with nebulised water.

nebulised water challenge. Again readings for calculation of thoracic gas volume and airway resistance were taken every 2–3 minutes until they had reached a steady baseline. Of the 20 infants rechallenged with nebulised water, 11 had received an initial challenge with nebulised saline. Nine infants remaining asleep after the second nebulised water challenge were rechallenged with nebulised water for a third time. Patients had electrocardiographic and oxygen saturation monitoring during the study.

Table 1 Nebulised normal saline:baseline lung function before and sGaw after challenge in 11 infants

Patient No	*Airway resistance ($cmH_2O/l/s$)*	*Baseline readings*		*sGaw after challenge ($/s/cmH_2O$)*	*% Change in sGaw from baseline*
		Thoracic gas volume (ml/kg)	*sGaw ($/s/cmH_2O$)*		
1	22	30	0·15	0·13	−13
2	17	39	0·20	0·22	−10
3	21	38	0·11	0·09	−18
4	24	24	0·18	0·21	16
5	15	27	0·27	0·25	−7
6	25	43	0·15	0·15	0
7	15	30	0·16	0·15	−6
8	14	30	0·16	0·15	−6
9	14	28	0·21	0·19	−9
10	34	30	0·13	0·13	0
11	26	33	0·14	0·15	7

CALIBRATION OF NEBULISER

The mass median diameter of the nebulised water aerosol and the nebulised saline aerosol were determined using a Malvern laser particle size analyser (Malvern Instruments model 3600). The nebulised aerosol passed through 56 cm of plastic tubing before reaching the face mask of the child. An exact replica of this was built including bends and was fitted to the nebuliser to simulute in vivo conditions. The nebuliser was run for two minutes and the nebuliser cloud pulled across the laser beam of the Malvern device by single stage impacter, run at a flow rate of 60 l/minute. The output of the nebuliser was calculated by weighing the nebuliser and the tubes before and after nebulisation. Each reading was repeated on eight occasions. Calibration of the nebuliser was rechecked after the study had been in progress for six months.

A paired *t* test was used to analyse results. Ethical approval was given by the Nottingham Hospitals ethical committee and informed parental consent was obtained for the studies.

Results

Technically satisfactory results were obtained in 88 of the original 100 infants. The percentage change in specific conductance (sGaw) from baseline after challenge with nebulised water in the 88 infants is shown in fig 1. After nebulised water 51 infants showed a greater than 20% decrease and only three showed a greater than 20% increase in sGaw. The effect of nebulised saline on lung function is also included. Of the 32 infants challenged with nebulised normal saline only one showed a decrease in sGaw of greater than 20%.

This paper concentrates on the 20 infants who were chosen for rechallenge with nebulised water. Eleven of the 20 infants had been challenged with nebulised normal saline. Baseline lung function before and after challenges is shown in tables 1–4. There was no significant difference between the baseline readings and those after nebulised normal saline. Also none of these infants showed a greater than 20% change from baseline sGaw after normal saline. The 11 infants challenged with nebulised saline showed a significant decrease in sGaw after challenge with nebulised water ($p<0·01$).

All but one of the 20 infants showed a 20% decrease in sGaw after initial water challenge (fig 2). After the second challenge five of the 20 infants showed a less than 20% change in sGaw (fig 2). All other infants showed at least a 20% decrease in sGaw after the second nebulised water challenge. Of the nine infants who stayed asleep to allow a third challenge all but one showed a 20% decrease in sGaw.

There was a small decrease in mean (SD) baseline sGaw between the first (0·19 (0·05)/s/cmH_2O) and the second water challenge (0·18 (0·05)/s/cmH_2O) and the third challenge (0·17 (0·04)/s/cmH_2O).

The mass median diameter of the normal saline and nebulised water aerosol were 5·0 and 4·8 μm respectively (geometric SD 1·7 and 1·8). The mean (SD) output per minute of the normal saline and nebulised water aerosol was

Table 2 First nebulised water challenge:baseline lung function before and sGaw after challenge in 20 infants

Patient No	*Airway resistance (cmH$_2$O/l/s)*	*Baseline readings*		*sGaw after challenge (/s/cmH$_2$O)*	*% Change in sGaw from baseline*
		Thoracic gas volume (ml/kg)	*sGaw (/s/cmH$_2$O)*		
1	22	28	0·15	0·11	−26
2	16	39	0·22	0·15	−31
3	21	38	0·11	0·08	−27
4	23	24	0·19	0·14	−27
5	15	27	0·25	0·18	−28
6	18	31	0·16	0·10	−37
7	15	20	0·30	0·21	−30
8	20	31	0·16	0·11	−32
9	19	28	0·22	0·13	−41
10	39	30	0·13	0·11	−16
11	26	33	0·15	0·11	−26
12	16	32	0·19	0·15	−21
13	26	32	0·24	0·19	−20
14	21	37	0·13	0·10	−23
15	27	33	0·12	0·08	−26
16	16	27	0·25	0·17	−32
17	16	26	0·24	0·15	−40
18	25	31	0·14	0·11	−21
19	22	37	0·16	0·10	−31
20	21	28	0·18	0·13	−28

Table 3 Second nebulised water challenge:baseline lung function before and sGaw after challenge in 20 infants

Patient No	*Airway resistance (cmH$_2$O/l/s)*	*Baseline readings*		*sGaw after challenge (/s/cmH$_2$O)*	*% Change in sGaw from baseline*
		Thoracic gas volume (ml/kg)	*sGaw (/s/cmH$_2$O)*		
1	21·5	31	0·15	0·12	−14
2	22	34	0·15	0·14	−6
3	21	36	0·11	0·08	−28
4	27	23	0·17	0·16	−6
5	17	27	0·23	0·21	−8
6	22	28	0·16	0·10	−27
7	13	20	0·33	0·23	−37
8	20	32	0·15	0·10	−33
9	22	27	0·21	0·12	−40
10	36	28	0·13	0·10	−24
11	27	31	0·14	0·11	−26
12	18	32	0·17	0·12	−29
13	26	17	0·26	0·19	−27
14	18	35	0·15	0·10	−23
15	28	32	0·12	0·06	−50
16	16	27	0·24	0·25	5
17	26	27	0·14	0·10	−29
18	23	31	0·16	0·12	−25
19	25	37	0·14	0·10	−29
20	23	27	0·18	0·13	−28

Table 4 Third nebulised water challenge:baseline lung function before and sGaw after challenge in nine infants

Patient No	*Airway resistance (cmH$_2$O/l/s)*	*Baseline readings*		*sGaw after challenge (/s/cmH$_2$O)*	*% Change in sGaw from baseline*
		Thoracic gas volume (ml/kg)	*sGaw (/s/cmH$_2$O)*		
6	22	28	0·16	0·12	−25
7	15	20	0·3	0·23	−24
8	21	33	0·16	0·11	−31
9	22	27	0·2	0·1	−50
10	36	28	0·13	0·12	−9
11	27	31	0·17	0·11	−36
18	25	32	0·14	0·11	−22
19	23	37	0·15	0·11	−27
20	23	27	0·18	0·12	−34

1·7 (0) and 1·9 (0) g/minute respectively. There was no significant change in nebuliser output and particle size when measured six months after initial calibration.

Discussion

Bronchoconstriction after nebulised water has been demonstrated in asthmatic children and adults and it has been found to be a sensitive and highly specific test for bronchial reactivity in asthmatic patients.[9] This study demonstrates that nebulised water may also cause bronchoconstriction in infants with a history of wheeze.

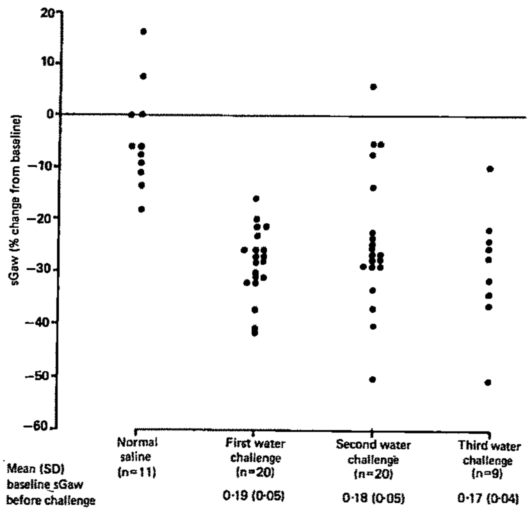

Figure 2 Percentage change from baseline of specific conductance after challenges with nebulised normal saline and water. Mean baseline specific conductance (/s/cmH$_2$O) before each challenge is also shown.

Where as no cut off is ideal for determining bronchial hyper-responsiveness we have chosen a decrease in sGaw of greater than 20% to be significant. This is based on results from a separate study where infants were repositioned while in the total body plethysmograph and lung function measured before and after. This gave an intrasubject coefficient of variation for sGaw of 10%. Therefore a change of greater than 20% is greater than twice the coefficient of variation of intrasubject change in specific conductance. Also in our study none of the 32 patients who were given nebulised saline had a decrease in sGaw of greater than 20%.

The aim of this study was to determine if wheezy infants were refractory to repeated nebulised water challenge. To determine the effect of antiasthma drugs it is important to know whether lack of bronchoconstriction after a further water challenge could be explained by a refractory period. The results of the 88 infants challenged with nebulised water were shown to indicate how the 20 infants were chosen. We do not feel we can analyse the results of the total group further. During our study period we found that it was impossible to say whether the infant was breathing through one of its nostrils, both of its nostrils, through its mouth, or both nostrils and mouth. Thus the delivery of aerosol to each infant may have been considerably different. We are now developing an accurate dosimetric technique for infant challenge studies. It appears from the study that 75% of our infants are not refractory to a second water challenge. It was interesting that eight of the nine infants who were challenged on the third occasion also showed greater than 20% decrease in sGaw. There was an overall decrease in baseline sGaw between challenges indicating a worsening of lung function through progressive challenge. This may have enhanced the effect of nebulised water in later challenges. Because resistance to airflow increases inversely with the 4th power of the radius, the response to bronchoconstrictor stimuli could have a dramatically greater effect on the airflow resistance in smaller airways of infants. In addition repeated challenge over a short period may have enhanced the bronchoconstrictor response by progressively decreasing the osmolality of fluid lining the airway. Lack of a consistent refractory period after nebulised water challenge has also been found by Mattolli *et al*[10] and Anderson *et al.*[11]

Only 11 of the 20 infants undergoing multiple nebulised water challenges were challenged with nebulised saline before nebulised water challenge. Ideally all 20 should have been challenged with nebulised normal saline. However we elected not to challenge nine of the infants with nebulised saline as this increased the study time and we had by then found that none of the initial 11 infants studied had shown a decrease in sGaw of greater than 20% after nebulised saline.

By measuring the slope of the mask pressure/box pressure trace and change in box pressure/flow trace it was possible to make multiple measurements and calculate airway resistance, thoracic gas volume, and sGaw during the study. Although measurements directly from the screen of the oscilloscope have been criticised, we feel that used in this context change in sGaw acts as a valid measurement to compare changes in lung function with repeated challenge.

The reproducibility of change in sGaw after nebulished water challenges was remarkably good. Because of this, observer bias needs to be considered and indeed the same observer made all of the readings and was aware of which challenges were being administered. However, during the study period a separate observer checked several of the readings. The second observer consistently underestimated the sGaw determined by the first observer by a mean of 15%.

The only conclusions that may be drawn from this study are that nebulised water may cause bronchoconstriction in infants with a history of wheeze and up to 75% of these infants show evidence of bronchoconstriction when rechallenged with a similar amount of nebulised water shortly afterwards.

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Bronchial provocation determined by breath sounds compared with lung function

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Abstract

Bronchial provocation testing with methacholine was undertaken in 15 children aged 5 to 8 years with obstructive lung disease, mostly asthma (13/15). The methacholine was inhaled during two minutes of tidal breathing in increasing concentrations. After each inhalation, lung function was measured and clinical signs recorded independently by two observers unaware of each other's results. The logarithm of the concentration of methacholine which caused wheezing over the trachea correlated closely with the logarithm of the concentration of methacholine causing a 20% fall in the forced expiratory volume in one second (FEV_1) but was 52% greater on average. At the end of the test there was a mean (SD) fall in FEV_1 of 33·3 (7·4)% and a fall in oxygen saturation of 5·2 (3·1)%. Bronchial provocation testing by listening for wheeze over the trachea is a safe technique, which correlates with objective measures of lung function in young children.

Methacholine challenge tests are commonly used for measuring bronchial reactivity in patients with clinical symptoms compatible with asthma.[1-3] This usual method requires consistent patient cooperation in performing repeated maximal expiratory manoeuvres or plethysmography and is only practical for adults and older children. Recently, we described a modification of the conventional technique in which tracheal auscultation was used in children instead of measurement of lung functions.[4] In that study we noted broad agreement between the concentration of methacholine causing wheezing (PCW) and that causing the forced expiratory volume in one second (FEV_1) to fall by 20% (PC_{20}) in older children (aged 6–15 years, mean (SD) 10·1 (2·9)) able to perform both tests but these studies were not undertaken in a blind fashion. The present study was designed to investigate further this association in a properly controlled manner in the youngest cooperative children and to incorporate observations on other physical signs and oxygen saturation.

Patients and methods

The patients were 15 children aged 5 to 8 years with a mean (SD) of 7·1 (0·9) years. Their pertinent details, resting lung function, and transcutaneous oxygen saturation are listed in table 1. All but two of the children had asthma and all were being treated in the paediatric pulmonology clinic. The mean (SD) baseline FEV_1 before the challenge was 92·9 (11·8)% predicted and no child had a value below 72%. Likewise no child was significantly hypoxic before the challenge with the mean (SD) saturation being 98 (1·9)%. Bronchial provocation with methacholine was requested as part of their routine evaluation and parental consent was obtained. All children were cooperative enough to perform maximal forced expiratory manoeuvres consistently. The methacholine challenge procedure used was the tidal breathing method described by Cockcroft *et al*[1] during the course of which physical signs and saturation were recorded and lung function measured. The lung function measurements were performed by a trained pulmonary laboratory technician (LC) with experience in bronchial provocation testing in children. The chest auscultations were all performed by the same physician (NN) who is experienced in paediatric pulmonology.

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Table 1 Anthropometric data, clinical diagnosis, and usual treatment

Patient No	*Age (years)*	*Weight (kg)*	*Height (cm)*	*Baseline FEV_1 (%)*	*Baseline transcutaneous oxygen saturation (%)*	*Diagnosis*	*Treatment**
1	7	26	125	83	95	Asthma	T, B
2	8	24	126	72	98	Asthma	T, S, B
3	8	27	131	75	97	Bronchiectasis	—
4	7	23	119	103	98	Asthma	B
5	7	22	119	85	98	Immotile cilia syndrome	B
6	5	19	116	89	99	Asthma	B
7	7	23	120	97	98	Asthma	T, B
8	8	26	126	104	100	Asthma	B
9	7	26	116	96	98	Asthma	C, B
10	8	23	126	88	100	Asthma	T, S, B
11	8	35	135	89	93	Asthma	T, S, B
12	6	26	120	121	100	Asthma	S, B
13	7	23	123	96	99	Asthma	C, B
14	7	22	121	94	97	Asthma	B
15	6	17	112	101	100	Asthma	S, B

*B, inhaled β_2 sympathomimetic agents as needed; T, slow release theophylline preparations; S, inhaled corticosteroid preparations; and C, sodium cromoglycate.

PROTOCOL FOR INHALATION CHALLENGE TESTS

All children avoided sympathomimetic bronchodilator treatment for at least eight hours before testing. Corticosteroids, slow release theophylline preparations, and sodium cromoglycate were continued unchanged. Details of medication are given in table 1.

Methacholine was delivered during two minutes of quiet tidal breathing from a nebuliser (Hudson, Temecula) containing 2 ml of test solution at the beginning of each inhalation. The aerosol was delivered into a face mask and inhaled through the mouth and nose. The nebuliser was driven by a compressor (Hand-E-Vent, Ohio Medical Products) with an output pressure of 15 psi yielding a rate of nebulisation of 0·20 ml/minute.

The children performed spirometry using a pneumotachygraph based system (Vitalograph Compact Spirometer, Vitalograph Medical Instruments). The highest value of FEV_1 from two technically satisfactory attempts was taken as the result. Measurements of baseline lung function were followed by two minutes inhalation of phosphate buffer solution (control). Spirometry was repeated after 30, 90, and 180 seconds. After this control inhalation, serial inhalations of doubling concentrations of methacholine were commenced, beginning with a concentration of 0·03 mg/ml and continuing every five minutes up to a maximal concentration of 16 mg/ml. If the fall in FEV_1 was between 15 and 20% the next increment in methacholine was by half the usual amount. For each concentration of methacholine, the measurements were performed as for the buffer solution.

Bronchial hyperreactivity by the standard method was defined as the methacholine concentration that caused a fall of 20% in FEV_1 from the best value after the buffer solution (PC_{20}). The PC_{20} was read from a log response curve by linear interpolation.

Breath sound auscultation using a regular paediatric stethoscope was performed for approximately 30 seconds beginning about 15–30 seconds after each measurement of lung function while the children were breathing quietly. Auscultation was performed over the trachea and both lung bases. However, for the purposes of defining the end point note was taken only of wheezing clearly heard over the trachea. In addition, a note was made at the time of each clinical observation of the presence of cough, intercostal retractions, and crepitations over the lung fields. Heart rate and respiratory rate were recorded and oxygen saturation was measured continuously by pulse oximetry (Nellcor Inc) with the lowest value free from motion artefacts being taken as the result.

Both PC_{20} and PCW were measured simultaneously, but in such a way that neither of the two investigators knew the results obtained by the other. The physician performed the auscultations without knowing the diagnosis, baseline lung function, the methacholine concentrations and the lung function post inhalation, and the technician did not know the clinical findings. It was decided before the study that the challenge should be halted when any one of the following conditions were met: (a) obvious wheezing heard over the trachea, (b) a methacholine concentration of 16 mg/ml, (c) a fall in FEV_1 greater than 50% from baseline, and (d) obvious dyspnoea. The methacholine concentration at which wheezing was first heard clearly over the trachea was taken as the result of the determination by auscultation (PCW). In the event, the end point of the challenge was wheezing heard over the trachea.

STATISTICAL ANALYSIS

Logarithmic transformation was used to describe the population results for PC_{20} and PCW. Comparisons between the two methods of evaluation in the individual subjects were made using the paired Student's *t* test.

Results

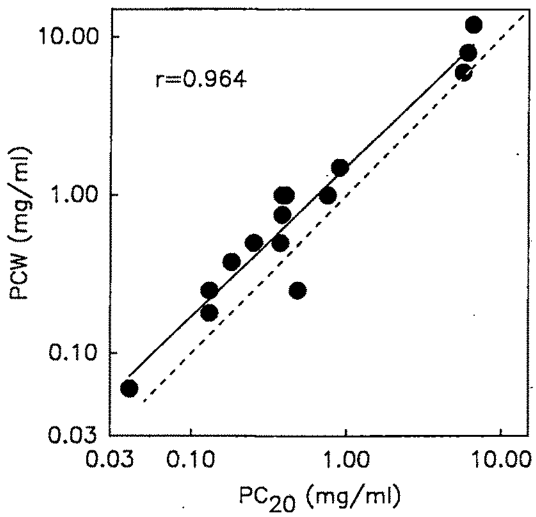
The individual results for PC_{20} and PCW are given in table 2. For the group as a whole the numeric equivalent of the mean of the $\log PC_{20}$ was 0·51 mg/ml with the mean +1 SD of 2·16 and the mean −1 SD of 0·12 mg/ml. The equivalent values for the PCW was 0·81 mg/ml with +1 SD and −1 SD values of 3·32 and 0·20 mg/ml. The difference between the $\log PC_{20}$ and logPCW was significant ($p<0·001$). The association between the PCW and the PC_{20} for the individual children plotted on a logarithmic scale is shown in the figure. There was an excellent correlation with the value for r being 0·964 but the PCW values were higher than the

Table 2 Individual results of PCW, PC_{20}, and the clinical signs which appeared when the PCW was reached

Patient No	PCW (mg/ml)	PC_{20} (mg/ml)	Δ FEV_1* (%)	Δ Respiratory rate* (%)	Δ Heart rate* (%)	Δ Oxygen saturation* (%)	Clinical signs†
1	0·06	0·04	−30	4	−4	−4	TW
2	0·18	0·13	−38	4	10	−1	TW, LW, cough
3	12·00	6·50	−39	18	25	−9	TW, crepitations, cough
4	0·50	0·37	−34	4	10	−3	TW
5	0·25	0·48	−21	28	2	−8	TW
6	1·00	0·75	−33	4	7	−8	TW, crepitations, cough, retractions
7	0·75	0·38	−34	4	7	−2	TW, LW, retractions
8	1·50	0·90	−26	0	8	−8	TW, crepitations, cough
9	1·00	0·40	−34	8	8	−6	TW
10	0·25	0·13	−49	12	7	−2	TW, LW, crepitations
11	0·50	0·25	−40	4	31	−3	TW, cough
12	8·00	6·00	−31	12	1	−3	TW, LW, cough
13	0·38	0·18	−42	16	−2	−8	TW, cough
14	6·00	5·60	−22	0	−2	−2	TW, LW, cough
15	1·00	0·38	−27	4	−9	−11	TW, LW

*Change from baseline at PCW.

†TW, wheeze over trachea and LW, wheeze over lung fields.



Association between PCW and PC_{20} in the individual children both plotted on logarithmic scales. The regression is shown by the solid line and the dashed line is the line of identity. The parallel shift of the regression line above the line of identity indicates that the PCW is on average 1·52 times as great as the PC_{20}.

PC_{20} values. The equation relating logPCW to $logPC_{20}$ is:

$$\log PCW = 0{\cdot}948 \times \log PC_{20} + 0{\cdot}182$$

which implies that the association is virtually linear (exponent of 0·948) and that PCW= PC_{20}×1·52 where 1·52 is the antilog of the intercept 0·182. The PCW was greater than PC_{20} in all but one child (table 2) and the mean (SD)% fall in FEV_1 at the methacholine concentration at which wheezing was first detected was 33·3 (7·4).

The physical signs and changes in respiratory and heart rates and oxygen saturation found on auscultation at the methacholine concentration at which wheezing appeared are also listed in table 2. The respiratory rate increased from baseline values by a mean of 8 breaths/minute (range 0–28) but only three children had a rise of more than 12 breaths/minute. Heart rate increased in 10 children, the maximum increase observed being 31 beats/minute, and decreased in the remaining five children with an overall mean rise in heart rate of 7 beats/minute. In eight children mild coughing had appeared coincidental with the wheezing, two developed mild retractions, and crepitations were heard in four. Oxygen saturation showed a mean (SD) decrease of 5·2 (3·1)% from the baseline value after the buffer inhalation. The lowest oxygen saturation recorded in any child was 88%. In all but one instance, where the oxygen saturation fell below 93%, there was an increase in the respiratory rate by more than 30 breaths/minute. In the one child, where the saturation fell to 89% but the respiratory rate only rose by 24 breaths/minute, there was obvious dyspnoea. All of the physical signs, changes in oxygen saturation, and changes in lung function responded promptly to the inhalation of salbutamol. There was no correlation between the changes in respiratory rate, heart rate, or oxygen saturation and either the PCW or the PC_{20}. In some patients mild wheezing over the lung fields, localised crepitations, or transient coughing appeared before audible wheezing over the trachea but these signs did not correlate with either the final PCW or the PC_{20}.

Discussion

This study has shown a high correlation between PC_{20} and PCW measured simultaneously in young children aged 5 to 8 years. In our previous study of children, who were on average three years older, we showed that the detection of tracheal wheezing by different observers was quite good with 80% complete agreement.[4] The results serve to validate further the method of bronchial provocation testing by means of tracheal auscultation for use in young children unable to cooperate with routine tests of lung function. The PCW induces a fall in FEV_1 of more than 20% on average. However, neither the severity of the obstruction nor the mild hypoxia in some patients was of any clinical significance and in no instance did the test result in anything more than mild, transient discomfort. In order to compare the severity of the airways obstruction when wheezing was first heard with that normally encountered at the end of a standard metacholine challenge to determine the PC_{20}, we examined the data from another 10 children of simliar age who had undergone a standard challenge. In these 10 children, whose mean equivalent of the $logPC_{20}$ (0·47 mg/ml) was very similar to that in the present study, the mean (SD) of the fall in FEV_1 at the end of their challenge was 30·6 (6·7)% which was not significantly different from the fall in FEV_1 in the present study at the conclusion of the challenge when wheezing was heard.

A decrease in transcutaneous oxygen tension in response to the inhalation of methacholine has been suggested by Mochizuki *et al* as a method of measuring bronchial reactivity as a result of a study in children with a mean age of 11 years.[5] They showed a good correlation between the methacholine concentration causing the first fall in transcutaneous oxygen tension and that causing the first rise in respiratory resistance. However, as they did not relate their observations to any other measure of bronchial reactivity or to the clinical condition of their patients it is difficult to evaluate the method they described. In the present study the decrease in oxygen saturation was small and did not correlate well with the PC_{20} or the reduction of FEV_1. To date we have performed over 300 tests using this method and have not needed to administer oxygen or give any additional treatment besides one inhalation of a β agonist bronchodilator at the end of the test.

In our previous study in older children we noted that in three out of the 10 patients the test had to be stopped because the FEV_1 had fallen by more than 20% before any wheezing had appeared.[4] In other children studied in this laboratory (personal observations) we also noted that the PCW was greater than the PC_{20} for asthma of similar severity. Thus comparing the PCW in 17 asthmatic children aged 6–8 years old with the PC_{20} in 34 asthmatic children of similar age and asthma severity, we found that the ratio $PCW:PC_{20}$ was 1·39. In the present study the ratio $PCW:PC_{20}$ was similar (1·52) for simultaneous measurements in the same children. When using the stepwise doubling concentration technique for bronchial provocation with methacholine, the greater concentration for the PCW represents one half step more than that for the PC_{20}.

In the standard steady state method of bronchial provocation described by Cockcroft and colleagues,[1] which we used for our study, the results are expressed as the methacholine concentration causing a 20% fall in FEV_1 (PC_{20}). Some investigators prefer to express the results as the total cumulative dose of methacholine received (PD_{20}). We therefore also calculated this parameter and the equivalent for the wheeze provocation study (PDW) and found that the correlation between them was very similar to that between PC_{20} and PCW:

$$\log PDW = 0{\cdot}991 \times \log PD_{20} + 0{\cdot}163$$

with a correlation coefficient of 0·961. This calculation implies that $PDW:PD_{20}$ is 1·46. In fact the simple comparison of PC_{20} (or PD_{20}) with PCW (or PDW) is not strictly fair as it is possible that wheezing would have been heard at a concentration of methacholine lying between the PCW value and the previous concentration. The calculation of PC_{20} (or PD_{20}) by extrapolation allows for such a situation. If the PCW were reduced to lie between the last two concentrations of the series this would have the effect of subtracting 0·15 from the log concentration and would reduce the mean difference between them to almost zero such that:

$$PCW = 1{\cdot}08 \times PC_{20} \text{ and } PDW = 1{\cdot}03 \times PD_{20}.$$

In conclusion we believe that the stethoscope can be used to detect wheezing over the trachea as the end point for bronchial provocation testing in young children during the quiet tidal inhalation of methacholine mixtures. In view of the observed mild hypoxia we think it prudent to suggest that the test should be performed by a trained physician, that the concentration of methacholine should be increased by half the usual amount when any of the clinical signs appears, and the test should be stopped if dyspnoea and/or tachypnoea appears, even if no wheeze is audible over the trachea.

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Compliance with treatment in asthma and Munchausen syndrome by proxy

V Godding, M Kruth

Abstract

Among 1648 asthmatic patients, 17 families (1%) were identified as having Munchausen syndrome by proxy. Ten families did not treat their children's, attacks or refused medical care, and seven exaggerated the severity of symptoms to obtain invasive investigations and treatment. All the families had disturbed psychosocial backgrounds. The abuse consisted mainly of neglect, in that necessary treatment was not given. In some cases a more direct form of abuse was observed, when useless and sometimes harmful investigations and treatment were given.

We conclude that medical control of the compliance of both parents and children is necessary in the management of childhood asthma.

Munchausen syndrome by proxy describes parental behaviour that creates the appearance of, or produces, physical illness in a child with harmful consequences to the child. It was first described by Meadow,[1 2] and is now well documented. It may be relatively common, but is frequently unrecognised.[1 3 4] It usually takes the form of the mother falsifying an illness, and presenting the child for medical assessment and care, often resulting in numerous procedures. It has been recorded in several childhood disorders including infectious, renal, and neurological diseases[5]; haematological, endocrine, and gastrointestinal conditions; and allergies.[6] It is difficult to diagnose and is often poorly identified and managed by health care professionals.[3]

There is still controversy about what constitutes the diagnosis with opinions ranging from simple neglect to active attacks on the child's health, or life, or both.[7] A recent approach suggested by Meadow is the concept of a range of types of Munchausen syndrome by proxy from perceived illness (symptoms perceived as illness by the mother) and trying one doctor after another, to enforced invalidism (the child is taught to become an invalid), and fabricated illness (R Meadow, Current research on Munchausen syndrome by proxy. Lecture, Catholic University of Leuven, Belgium, March 1990).

During our three years' experience of joint paediatric/child psychiatric consultations with severely asthmatic children and their families, we became convinced that some parents' behaviour toward their children's disease was child abuse within the range of Munchausen syndrome by proxy.[8]

Asthma is a chronic disease in childhood, the prognosis and evolution of which is dependent on correct management. Poor compliance with treatment among asthmatic children has been well documented and occurs in 10–50% of patients.[9–13] We diagnosed some non-compliant families of asthmatic children as having Munchausen syndrome by proxy because the parents lied or concealed information when describing their child's symptoms, or treatment, or both, and because of the harmful impact this had on the child's mental and physical wellbeing.

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Patients and results

We encountered 17 families (of 1648 asthmatic patients) whose management of asthma involved falsifying symptoms or manipulating treatment, or investigations, or both. In 10 cases this resulted in increased severity of the disease, and in seven in useless investigations and treatment being carried out. All these patients had been referred to us because their asthma was poorly controlled and all had previously consulted other departments of paediatric or respiratory diseases.

The 17 families that abused their children were divided into two groups depending on their attitude to treatment. Ten undertreated the children. There was a definite worsening of the children's asthma and as a result a need for attendance at the emergency department or hospital admission, invasive investigations, intensive care, and other aggressive medical treatment (table 1). Seven overtreated their children. There was no worsening of the child's asthma, but unnecessary investigations, admissions to hospital, and treatment were engineered by manipulating the medical system (table 2). After diagnosis in the hospital department originally consulted, all these families had repeatedly received correct medical information about the prognosis and management of asthma.

FAMILIES THAT UNDERTREATED THEIR CHILDREN

Ten families comprising 11 children were encountered within a three year period. The mean (SD) age of the children was 7·5 (2·8) years, and there were two girls and nine boys. Ten of these 11 patients were described by their parents as severe asthmatics who had daily or weekly attacks. One patient was described as asthmatic, though he had type III recurrent alveolitis. All the families abused their children at some stage of management.

Table 1 Families that undertreated children

Case No	*Sex*	*Age (years)*	*Perpetrator*	*Behaviour*	*Child's medical condition*	*Intervention*	*Result*
1	F	8	Parents	No treatment, no medical advice for four years (weekly to daily attacks), child was told she would die suddenly	Severe asthma (daily attacks)	Family therapy for parents, intensive medical treatment for child	Good
2	M	6	Mother	Acute and preventive treatment not given when necessary, wrong treatment given	Severe asthma	Intensive treatment	Death at 17 years old
3	M	8	Grandmother	Acute treatment not given, treatment given, preventive treatment not given	Severe asthma and chronic airway's obstruction	Joint consultation	Good
4	M	4	Mother	Acute treatment not given, wrong treatment given, preventive treatment given, then stopped	Frequent emergency hospital admissions for severe asthma or bronchitis	Joint consultation	Tried many doctors
5	M	10	Father	Father forced him out of emergency department where he was treated for an acute attack	Immediate worsening, and bad control of asthma	Police called	No follow up
6	M	4	Mother	No acute treatment given, no medical help requested for severe attacks	Severe asthma, absent from school	Joint consultation	Good
7 8	M F	8 12	Mother	No acute treatment when necessary, wrong treatment given, preventive treatment stopped, no medical help requested when necessary	Severe asthma, poor school attendance	Joint consultation, work with general pratitioner, intensive education programme	Good
9	M	6	Mother	Acute treatment not given, wrong treatment given, preventive treatment stopped, no medical help requested when necessary	Severe asthma	Joint consultation, work with general practitioner	Good
10	M	5	Mother	Acute treatment not given, preventive treatment stopped	Severe asthma, absent from school	Joint consultation	Tried many doctors
11	M	12	Mother	Actively exposed to pigeons, although the parents pretended all the pigeons had been given away	Type III recurrent alveolitis (pigeon fancier's lung), severe restrictive airway's disease, absent from school	Joint consultation	Good medical results

Table 2 Families that overtreated children

Case No	*Sex*	*Age (years)*	*Perpetrator*	*Behaviour*	*Child's medical condition*	*Intervention*	*Result*
12	F	4	Grandmother	Manipulated doctors to obtain potent drugs (antibiotics or antiemetics) or invasive investigations	Mild asthma, a year's treatment with antibiotics and antiemetic drugs, invasive investigations	Joint consultation, work with general practitioner	Stable for more than two years, tried many doctors
13	F	11	Mother	Emergency hospital admissions for invented symptoms (fever, cough, asthma), obtained investigations and treatment for no reason	Poor school attendance and results, mild asthma, unnecessary hospital and treatment admissions	Joint consultation	Stable for more than a year, tried many doctors
14	F	10	Mother	Symptoms falsified, common cold described as asthma or bronchitis to obtain prescriptions for potent drugs and invasive investigations	Mild asthma, invasive treatment and restriction of sporting activity	Joint consultation	Good medical progress
15	F	8	Mother	Mild symptoms presented as severe asthma, emergency admissions, potent drugs given (antibiotics or steroids)	Mild asthma, invasive treatments, absence from school, no outdoor activities, depression	Medical follow up	Good progress
16	M	7	Mother	Symptoms exaggerated, considered by mother to be mentally retarded though normal, potent drugs given	Mild asthma, educational retardation	Joint consultation	Good progress
17	M	6	Mother	Symptoms exaggerated, manipulation of doctors to obtain invasive investigations including blood tests and *x* ray pictures	Invasive investigations and treatments, mild asthma	Joint consultation, work with general practitioner	Tried many doctors
18	M	10	Mother	Manipulation of doctors to obtain invasive treatment: a year's course of oral steroids for stable, moderate asthma	Weight gain, growth retardation, moderate asthma	Joint consultation	No treatment with steroids, stable moderate asthma

Treatment during the acute attack

In seven of the 10 families the prescribed treatment was not given to the child during an attack. In six of them a large number of ineffective treatments were used such as a ventilator (blowing dust), nebulisation of distilled water, aspirin, cold syrups, very small doses of bronchodilator syrups, and cold packs on the chest, all to no effect. None of these families spontaneously mentioned their behaviour. All seven children had severe asthma; one died at the age of 17 during his fifth episode of status asthmaticus, three had chronic airway's obstruction, and five had frequent emergency treatment or admission to hospital.

Preventive treatment

In five of the seven families who did not give the correct treatment during the acute attack, the preventive treatment was also not given to the child, although the parents pretended that it was. The following drugs were withheld: beclomethasone (n=3), salbutamol (n=4), and sustained release theophylline (n=5). To ascertain that preventive treatment had effectively been withheld we interviewed the children about the first two drugs, and then measured the theophylline concentration in the blood. The children were asked in front of the parents to write down, or draw, what they received as daily treatment. The parents were then asked about the missing drugs. Monitoring theophylline concentrations in the blood was useful for the five patients concerned, and on several occasions showed that none had been given.

Seven of the 10 families said they had been avoiding known allergens when they had not. In one case a 10 year old boy had had three acute episodes of type III alveolitis (pigeon fancier's lung). He had developed severe symptoms of weight loss (6 kg), high fever, and dyspnoea, and had spent a long time in hospital before he recovered. The parents, who owned some 40 pigeons that lived in their home, had been informed on several occasions about the aetiology of their son's disease. They had stated that all their birds had been given away, when all the time they were hiding the 40 pigeons in the room next to the patient's room, and this was only discovered when the hospital social worker was sent to visit the house after the third acute attack.

Withholding of treatment

In one case no treatment at all was given and no medical advice was sought for a period of four years for a child who was having daily or weekly attacks. She was openly told by her family that she was at high risk of sudden death (table 1). She developed severe asthma and had two episodes of status asthmaticus.

Another patient was forced out of the emergency department by his father while he was being treated with oxygen and nebulised salbutamol for an acute attack. It was necessary to ask the help of the police to get the child into the emergency department at another hospital.

Family history

The family histories showed that at least one parent in each family had had a chronic medical problem during their own childhood. The most common was asthma (eight mothers, two fathers, and one grandmother). Siblings were affected in half the families. In addition, six of the 10 mothers were clinically depressed, the parents had recently divorced in three families, a close relative had died in one, and the mother of another child was known to abuse morphine.

Family behaviour with doctors[3]

Two of the 10 families were always seeking medical advice. Five of the families refused to allow doctors to see their children; these are the families that we consider to be at high risk, because they do not attend follow up appointments, do not call a doctor if the child has frequent attacks, and nevertheless are always seeking different treatments. The remaining three families disliked doctors and threatened them.

FAMILIES THAT OVERTREATED THEIR CHILDREN

During the three year period we encountered seven families who abused their children; there were four girls and three boys, with a mean (SD) age of 8 (2·5) years. These families behaved as if they wanted their children to remain chronically ill. The respiratory consequences were not as severe as those found in the undertreated children, but there was health abuse that directly affected school attendance and the child's psychosocial development as well as subjecting the child to unnecessary, expensive, and potentially harmful investigations and treatments.

Family behaviour

All these families exaggerated their descriptions of the child's symptoms—for example, a mild symptom like a non-productive cough was described as acute asthma. Some parents deliberately falsified the symptoms, mentioning high fever, vomiting, and dyspnoea, that had never occurred. All seven families were used to manipulating the medical system to obtain prescriptions for potent drugs like antibiotics, antiemetics, bronchodilators, and oral corticosteroids. In four of the seven families the strategy was to call the general practitioner on duty (who did not know the patient) and tell him that the child was being treated for severe asthma, and had to receive antibiotics, antiemetics, oral corticosteroids, or bronchodilators as soon as he began to cough. Three of the families used to present the child in the emergency department of two or more hospitals with exaggerated or invented symptoms.

Five of the patients underwent useless and potentially harmful investigations such as blood tests, skin tests, and *x* ray examinations on several occasions. Six of the families overused medication—for example, giving oral corticosteroids or antibiotics for a common cold.

Family history

The family histories showed that six of the mothers and one of the grandmothers had had asthma as children. Five of the seven mothers were clinically depressed, and the grandparents of one child had recently died. One mother was a single parent living with her own parents. Five families were always seeking medical advice, one family would not allow a doctor to see the child, and one family disliked and threatened doctors.

Discussion

In all 17 cases there was evidence that the parental mismanagement of the child's asthma constituted child abuse. In the families that undertreated their children the abuse consisted of providing no relief to the child during an attack, although they knew how to stop it. An attack of asthma is harmful to a child, both physically and mentally. The abuse by the families that overtreated their children consisted of imposing potentially harmful and useless investigations or treatments, or both, on the child by fabricating or exaggerating the disease.

In the first group the persistent severity of the symptoms, which remained unresponsive to the (supposed) treatment, led to the diagnosis of severe asthma. It can be assumed that most of these patients would have reacted differently with correct management. Severe asthma was the fabricated illness, although these children may have had mild or moderate disease. In the second group the disease was factitious; the symptoms described by the parents never existed. Indeed, the illness was made to seem more real to the parents by the invasive investigations and treatments imposed on the child. The severity of the asthma was factitious, but the children really had mild asthma.

Most of the parental behaviour concerning asthma management can be described as neglect. In the 10 families that undertreated children, eight mothers did not treat the attacks at all, and two parents refused necessary medical care. Five mothers also withheld the preventive treatment. The disease was actively induced in cases where parents used ineffective treatments (with a direct worsening of the attack) or provided active contact with the allergen. In the seven families that overtreated their children, the parent's behaviour consisted of actively inducing the useless investigations and treatments. These cases of parental mismanagement of childhood asthma illustrate a parenting disorder. There was a disturbed psychosocial background in all 17 families.

Pathogenic hypotheses have been proposed by several authors. When describing the illness of the child, the mother (or grandmother) receives much attention and respect from the medical world and from her own surroundings. This need for medical attention can lead to so called 'doctor addiction'.[2] Through the illness the parent can also maintain a symbiotic relationship with the child,[14] which may explain why the syndrome is often diagnosed in young families in which children are beginning to develop their own personalities. Abuse can also occur in cases of marital conflict. The continuous illness of the child diverts attention from the marital conflict—for example, the two parents are reunited in their common care for the sick child.[1]

The care and devotion that the abusing parent gives to the sick child often wins for that parent the love that was lacking in their own early childhood. Recent research has shown that exploitative dominance of a submissive child by a parent does occur.[15] Most of the parents that abused their children were themselves abused as children. The mothers often tried more direct ways of expressing their own distress before abusing their children, including complaining of depression and psychosomatic symptoms or suicidal thoughts, or by overusing drugs themselves.[5 7]

All these patterns have been associated with other psychosocial disturbances. The specific precipitating factors that lead to Munchausen syndrome by proxy in these disturbed families were physical vulnerability (bronchial hyperactivity or allergy), the relationship between the family and the doctor, and the unwilling collaboration of the medical system.

Conclusions

Parents' management of asthma as a chronic physical disease in a child may develop into Munchausen syndrome by proxy. In three years of joint consultations about 1648 patients with asthma we found management of asthma that constituted child abuse in some 1% of asthmatic patients and their families. Early recognition of behaviour that falls within the accepted range of the syndrome may prevent medical professionals from becoming unwilling collaborators in abuse. Munchausen syndrome by proxy should be considered as a differential diagnosis in severe asthma, or if stable moderate asthma suddenly becomes worse.

Checking compliance of both parents and patients should be regarded as an essential part of a doctor's duty if child abuse is to be recognised and the child's health protected.

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Commentary

The term Munchausen syndrome by proxy was used initially as a headline to highlight underrecognised forms of child abuse. That journalistic licence has been justified by the discovery of many children being subjected to suffocation, poisoning, and other extreme physical abuse. The term has also permitted child care workers and legislators to intervene more easily under the cover of Munchausen syndrome by proxy in some serious complex cases of emotional abuse in which mothers were not physically harming their children but were ruining their lives with stories of false illnesses.

The term, and particularly its overuse, has led to problems (at times I have regretted coining it). Many lawyers, social workers, and sometimes doctors, seem to regard Munchausen syndrome by proxy as an identifiable disorder that afflicts certain women; it is common for the perpetrator to announce proudly 'I've got Munchausen syndrome by proxy, and the judge says I needn't go to prison providing I see the specialist and have treatment.'

A more worrying issue for the paediatrician is how readily factitious illness should be identified, and how readily child abuse procedures should be invoked. Most of us use our illnesses to our own advantage to gain sympathy, freedom from unpleasant tasks, and some material benefits (if only some self indulgence). Chronic illness, with all its burdens, also bring benefits: certain allowances and privileges. Similarly, mothers will use illness to their own advantage, and because illness may bring both emotional and material advantage to that mother she will occasionally exaggerate the illness and deceive or act in ways that are mildly harmful to the child for her own advantage.

Just as familiar to paediatricians are the many mothers who, because of their own anxieties and uncertainties, perceive symptoms in their child that others cannot observe. Though the stories of illness that they relate to the paediatrician may cause needless investigation and unpleasantness for the child, it would be rare to classify such a mother's behaviour as child abuse.

Godding and Kruth claim that they have identified 17 families displaying behaviour of Munchausen by proxy within a large clinic serving nearly 2500 families. They do not define their terms precisely, and in particular their cases do not have the hallmark of Munchausen syndrome by proxy—that the child, when away from the parents, is better. Readers may feel that the authors are wrong to classify the 17 cases in this way. Some are non-compliers. Yet paediatricians are aware that common reasons for undertreatment and non-compliance are our failure to spend enough time with our patients or to adapt and present our management strategies in a way that is acceptable and appropriate to the families' beliefs and culture. At other times we may be inappropriately optimistic in our expectation for families to comply with demanding and frequent treatments—for example, requesting that a mother who relies on 20 cigarettes a day should stop smoking altogether. In a clinic in which more than 2000 children with asthma are seen I would expect most to be non-compliant to some extent. Similarly a large proportion will exaggerate symptoms or overuse treatment for other reasons. Such behaviour is normal.

It is noteworthy that the authors identify only 17 children, and it is because of that—and my knowledge of their work—that I believe that they are probably right to apply the label Munchausen syndrome by proxy to that small minority of their patients. These seem to be extreme cases in which the parental actions are severely interfering with the child's healthy development. They are not merely those cases by which we are irritated: the parents who demand a free telephone because of their child's extreme breathlessness and blue spells (which only the mother sees); the family whose child always has a normal peak flow at the clinic yet who has, because of the child's asthma, a 'disabled' car parking badge that enables them not only to park outside Marks and Spencer but—even more annoyingly—within the hospital grounds (while the doctor seeing them gets his car's wheels clamped).

In any chronic childhood illness there will be a small minority of parents whose behaviour, in terms of compliance and non-compliance, amounts to child abuse. I believe it is correct to be prepared in these extreme cases, when expert help and persuasion has failed, to confront the issue as one of child abuse and to invoke child protection measures including, if necessary, resort to the courts.

As with all child abuse it is important to stand back and work out just how much the parents' actions are jeopardising the child's present happiness and future health and development, and to consider carefully the consequences of intervention.

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Attitudes of paediatricians to HIV and hepatitis B virus infection

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Abstract

There is a recent upsurge of interest among health care professionals regarding the risk of accidental occupational exposure to HIV virus. We evaluated knowledge of virus carriage prevalence, needlestick injuries, venepuncture practices, and glove use among paediatricians in Wales and South West Regional Health Authorities. We also attempted to evaluate hepatitis B immunisation uptake in this group. Paediatricians have traditionally been considered a low risk group in the context of accidental occupational exposure to these viruses.

We targeted a four point questionnaire at 221 paediatricians. Results suggested that despite recent increasing concern about these viruses, that is reflected in the amount of medical literature recently published, and the issuing of Department of Health guidelines on venepuncture, knowledge of prevalence of HIV and hepatitis B carriage rates, and hence assessment of risk magnitude, was surprisingly poor. Safe venepuncture practices were not widely used. In the 12 months before receiving the questionnaire 55% had suffered a needlestick injury with only 10% reporting the fact. Hepatitis B immunisation uptake was highest in the junior grades (but this does not necessarily mean those at greatest risk). There were many inconsistencies between the clinicians' perceptions of risk and their practices.

As the virus attains a firm hold in the heterosexual population paediatricians by virtue of the nature of venepuncture in children will almost certainly see their risk of acquiring HIV/hepatitis B viruses secondary to accidental occupational exposure increase over the next decade. Without an improvement in current knowledge of carriage prevalence in high risk areas and alteration in venepuncture practices/hepatitis B immunisation uptake some will unfortunately, though avoidably, contract these bloodborne viral infections.

Accidental occupational exposure to bloodborne viruses including HIV/hepatitis B is to be increasingly expected as investigative medicine proceeds and more difficult procedures are undertaken. There has been a recent upsurge in interest of the hazards of accidental occupational exposure to these viruses among surgeons[1 2] and anaesthetists.[3]

These two groups have traditionally been considered the groups most at risk of acquiring these viruses secondary to accidental occupational exposure. Paediatricians have been considered to be among those at low risk with very little work having actually been undertaken in this group.

There are improved venepuncture techniques now more widely used among adults and difficulties in using gloves in paediatric practice. Because of this and because of recent evidence that HIV is occurring increasingly among the heterosexual population,[4] it was felt that paediatricians may well find themselves at increased relative risk.

A survey was undertaken by questionnaire of paediatricians from hospitals accepting acute paediatric admissions in Wales and South West Regional Health Authorities. The aim of the questionnaire was to assess the following four aspects. (1) Knowledge of prevalence of HIV seropositivity in a high risk area and hepatitis carriage rate (an assessment of risk magnitude). (2) Needlestick injury: frequency of and related actions of the paediatrician. (3) Venepuncture practice: including the use of gloves in clinical practices. (4) Hepatitis B immunisation uptake among paediatricians.

Method

The questionnaire was targeted at 221 paediatricians in two regions, the Wales and South West Regional Health Authorities. A single mailing was undertaken without reminders. The questionnaire was designed so that answering entailed encircling or underlining the answer the paediatricians felt to be correct.

QUESTIONNAIRE (SEE APPENDIX)

A total of 20 questions (17 stem questions) were posed and this included two questions asking about perception of current risk and whether or not this was likely to increase. This enabled us to divide the assessment of results into two groups (in fact of similar size and with a similar ratio of staff from all grades).

Results

We received a reply from 127 (57·5%) of the 221 paediatricians in the two regions. There were 31 consultants (24·5%), 27 paediatricians of middle grade (21·0%), and 69 senior house officers or junior grade (54·5%). This return rate is quite consistent with previous mail surveys reported by Cartwright among hospital medical personnel.[5] Our survey was based on a single mail shot with no reminders. The decision not to send reminders was based on two reasons. (1)

Internal rotation of staff may well have taken place and as the survey was anonymous then there was a real risk of data duplication. (2) A short term perception of disease risk was necessary to examine practices in those groups with different risk perceptions. With an aggressive public education campaign occurring throughout the latter part of the last year, long term risk perception may well have been altered and hence affected analysis of results.

The knowledge of HIV seropositivity prevalence in high risk areas was very poor with only 23% correct overall. The highest number of correct answers was among middle grades (30%) and lowest among senior house officers (17%). A similar result was obtained for prevalence of hepatitis B carriage. Of the total questioned 93% confirmed the greater infectivity of hepatitis B compared with HIV (97% among senior hours officers compared with 87% among consultant grade staff) (see table 1).

Needlestick injuries had been suffered by 85% of those questioned sometime during their career and 55% in the last year. Many had suffered more than one needlestick injury but only seven out of 70 (10%) reported these events. Of those that reported these events only four out of seven (57%) had had antibody concentrations checked. Needlestick injuries were equally common among junior and middle grade staff.

General glove usage was low in general paediatric settings (35% of total sometimes/always wore gloves). They were used most in the higher age group children. Gloves were frequently used in accident and emergency departments but used most in the delivery suite area (56 out of 114 (49%) in accident and emergency and 91 out of 112 (81%) in the delivery suite). This suggests that safety measures take up a much higher profile in these settings. When asked about risk perception at the present time 55 out of 127 (43%) felt it was low and increasing whereas 48 out of 127 (38%) felt it was high and increasing (see tables 2 and 3).

Unfortunately resheathing of needles was always/sometimes undertaken by 101 out of 126 (80%): 40/126 (32%) always and 61/126 (48%) sometimes. This put the doctors at very high risk of accidental occupational exposure. Formal instruction on phlebotomy technique had been received by 38 out of 127 (30%). In the high risk perception group, interestingly, only 17% had received formal instruction (compared with 40% in those who perceive a low current risk).

Overall hepatitis B immunisation uptake was 90 out of 127 (71%) of paediatricians. However, this represents an immunisation uptake of 88% among senior house officers compared with 60% of middle grade staff and 42% consultants. Only 58 out of 90 (64%) of those immunised had had antibody concentrations checked. The reasons for non-immunisation were varied and were not clear.

Nearly all (95%) paediatricians expected their relative risk of acquiring HIV/hepatitis B as opposed to other groups to increase. This was against a group of 38% who already perceived themselves to be at high risk of acquiring hepatitis B secondary to accidental occupational exposure.

When looking at the group who already perceived a high risk (and which would increase in the future) the following was found. (1) Altogether 56% had had needlestick injury in the last year but only 11% of these had reported it (compared with 51% and 14% reporting in low

Table 1 Paediatricians' assessment of risk magnitude and knowledge of HIV seropositivity in high risk area and hepatitis B carriage in the UK. Results are number giving correct answer/number of respondents (%)

	Consultant	*Middle grade*	*Senior house officer*	*Total*
Prevalence of hepatitis B carriage	10/31 (32)	12/27 (44)	19/69 (28)	41/127 (32)
Prevalence of HIV seropositivity[12]	9/31 (29)	8/27 (30)	12/69 (17)	29/127 (23)
Infectivity of HIV/hepatitis B	27/31 (87)	23/26 (88)	66/68 (97)	116/125 (93)

*Table 2 Evaluation of needlestick injury and safety practices amongst paediatricians. *Results for glove usage are number who sometimes or always wore gloves/number of respondents (%)*

Risk perception	*No (%) who had needlestick injury (in one year)*	*No (%) of those with needlestick injury who reported it*	*Glove usage at different ages**				
			Delivery	*Neonatal*	*Infant*	*Child*	*Accident and emergency*
High (current) and increasing (n=48)	27 (56)	3 (11)	35/43 (81)	14/47 (30)	17/48 (35)	21/48 (43)	24/42 (57)
Low (current) and increasing (n=55)	28 (51)	4 (14)	40/49 (81)	19/52 (36)	20/52 (38)	22/53 (41)	21/52 (40)

Table 3 Evaluation of needlestick injury and safety practices among paediatricians

Risk perception	*No (%) who used Vacutainers**	*No (%) who had phlebotomy instruction*	*No (%) who resheathed needles*	*No (%) who had hepatitis B immunisation*
High (current) and increasing (n=48)	13 (27)	8 (17)	12 (always) 22 (sometimes) } (71)	37 (77)
Low (current) and increasing (n=55)	18 (33)†	22 (40)	19 (always) 26 (sometimes) } (82)	40 (73)

*Becton-Dickinson.
†Only 54 respondents.

risk group); $\chi^2=0\cdot294$, $p>0\cdot05$. (2) A total of 77% had received hepatitis B immunisation (compared with 73% in those who perceived a low risk); $\chi^2=0\cdot26$, $p>0\cdot05$. (3) Altogether 39% always/sometimes used gloves in general paediatric settings (compared with 41% in low risk group); $\chi^2=0\cdot0087$, $p>0\cdot05$. (4) A total of 71% resheathed needles (compared with 81% in low risk group); $\chi^2=1\cdot73$, $p>0\cdot05$. Statistical analysis of these figures showed no difference between the groups.

Discussion

As clinicians involved in paediatric practice we, the authors, felt that an assessment of this nature was long overdue. With changes in adult venepuncture practices occurring during the last decade, though not easily applicable to paediatric venepuncture, it was felt that paediatricians largely seem to ignore the risks that venepuncture poses to themselves.

Very little work has been done among paediatricians, though they were mentioned in work by Levy *et al.*[6] Generally they have been considered to be a low risk group with much lower risks than surgeons, anaesthetists, and nursing staff in accident and emergency departments. This may well remain the case at present, though with changing epidemiological characteristics of HIV and more sophisticated techniques used among small infants and children in intensive care settings the risks may well alter. The current world hepatitis B carriage rate is in the order of 200 million people[7] with the UK carriage rate in the order of 0·1–0·5%.[8] Seroconversion after contaminated needlestick injury with hepatitis B is in the range of 5%[9] and 30%[10] and for HIV in the order of 0·5%.[11] This must be considered against a background of increasing numbers of invasive procedures undertaken in children and the all too often sight of the junior paediatrician learning the trade with a hand covered in blood from his first few heelprick attempts. In many ways this scenario (prolonged and frequent skin contact with blood) is as disturbing as the failure to report needlestick injury.[6]

The lack of uniformity of HIV prevalence meant it was difficult to choose a representative figure. We therefore (in view of the fact that we were assessing paediatricians) chose the survey of Guthrie test analysis by Peckham *et al* in a high risk area.[12] This put a seroprevalence figure of 0·24/1000 which represented the at risk population to a paediatrician practising in this region in the delivery suite but *not* the figure for true HIV infection.[13] This was also not the figure that any of the paediatricians we assessed were facing but with a continuous change of staff (particularly junior grade and locum staff) a junior doctor could find himself working in a high risk setting at any time in his career.

There has been quite widespread education in the media and by occupational physicians both nationally and in the relevant areas over the last few years. Our results, however, suggest that knowledge pertaining to HIV seropositivity and hepatitis B carriage (and hence magnitude of risk assessment) is poor. More than two thirds of our respondents were out by a factor of 10 or more in their estimation of prevalence. This contrasts quite considerably with the better general knowledge that health care workers have compared with the public regarding HIV transmissibility, etc.[14] Disturbingly venepuncture practice among all groups of paediatricians leaves a lot to be desired.

Despite recent issuing of guidelines from the Department of Health regarding venepuncture[9] more than 75% of junior paediatricians still resheath needles. This if reflected nationally would put many at risk of HIV in the future as well as hepatitis B (as even in those immunised there is a 4%–10% risk of attainment of inadequate antibody concentrations).[15 16]

The universal failure to report needlestick injury must surely be improved with strenuous attempts by occupational physicians to get the message across. We are aware of a similar situation in the USA where McCormick and Maki noted the apparent failure of physicians to report needlestick injury in 1981. Over a four year period in a large American centre with a turnover of 500 house grade staff annually only one needlestick injury was reported.[17] Adequate time must be allowed from routine work to attend the occupational physician and obtain advice after a needlestick injury. The actual reasons for both non-reporting needlestick injury and non-hepatitis B immunisation uptake are not clear. In our study it appeared that higher risk perception did not necessarily mean safer venepuncture practices.

Protective measures such as hepatitis B immunisation is low among those most often asked to undertake the difficult procedure. This needs to be corrected and a lesson learnt from the more junior counterparts. Hepatitis B immunisation alone is not sufficient reason for not reporting needlestick injury (it should not engender a feeling of false security).

Usage of gloves must be encouraged (they can protect against blood contact even if they have limited use in preventing needlestick injury) in all potential high risk situations and in all difficult procedures. The design of a thin but durable glove for the use of neonatal paediatricians would be helpful. The problem of universal implementation is likely to be one of cost (possibly an overall 40% increase in isolation material budget for universal implementation).[18] It is most desirable that juniors get simple clear instruction on venepuncture technique from their senior colleagues and an experienced nurse helps to hold the child especially in the first few weeks of a job.

It has been estimated that approximately 2% of people infected with hepatitis B die of the infection,[19] and one half of those infected with HIV will have developed AIDS within six years.[20] Hopefully this is enough of a risk for paediatricians to take note and alter their venepuncture practices, hepatitis B immunisation status, and basic attitudes to these viruses in the workplace. The danger is that paediatricians will still consider hepatitis B and HIV as 'adult diseases' for much too long before altering practices that will put themselves at risk of acquiring these viruses secondary to accidental occupational exposure. We hope that this limited study will have highlighted the problem facing paediatricians as regards to their attitudes to these viruses in the workplace and will lead the way for further more extensive studies of the subject.

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Appendix
Study of venepuncture technique, knowledge of factors affecting occupational exposure to hepatitis B and HIV virus, and uptake of hepatitis B vaccination among paediatricians in Wales and South West England

Current position in NHS:

Please underline or encircle the answer(s) *you feel to be correct*

Hepatitis B/HIV virus:

(1) The current estimate of hepatitis B carrier in the UK at present is in the order of:	(1) 1 in 1000 (2) 1 in 10 000 (3) 1 in 100 000
(2) A recent report in the *Lancet* testing HIV seropositivity in 114 515 Guthrie tests showed a positive rate in the Thames' regions of approx:	(1) 1 in 5000 (2) 1 in 50 000 (3) 1 in 500 000
(3) Which virus is thought to have higher infectivity?	HIV/hepatitis B
(4) As a paediatrician my current risk of attaining hepatitis B secondary to accidental occupational exposure is (relative to other hospital doctors):	(1) Low (2) High (3) Don't know

Needlestick injuries:

(1) Have you ever had a needlestick injury?	Yes/no
(2) How many have you received in the last year?	1/2/over 3
(3) Did you report these incidents?	Yes/no
(4) If so, was action taken?	(1) No (2) Yes, hepatitis B antibody (3) Yes, hepatitis B immunisation (4) Yes, HIV antibody checked

Phlebotomy technique:

(1) When taking blood do you use gloves:	
(a) In neonates	Always/sometimes/never
(b) In infants	Always/sometimes/never
(c) In children	Always/sometimes/never
(2) Have you received instructions in phlebotomy technique?	Yes/no
(3) When taking blood do you use the *Vacutainer* system in infants/children?	Always/sometimes/never
(4) When attending a delivery on delivery suite, do you wear gloves?	Always/sometimes/never
(5) When attending an injured child in the accident department, do you wear gloves?	Always/sometimes/never
(6) Do you resheath needles after use?	Always/sometimes/never

Hepatitis B immunisation:

(1) Have you received hepatitis B immunisation?	Yes/no
(2) If *no* to (1), is the reason for this?	(1) 'Can't be bothered' (2) See little risk (3) Worried regarding vaccine (4) Never offered vaccine (5) Other
(3) If *yes* to (1) have antibody levels been checked?	Yes/no

Summary:

Do you feel that the relative risk to paediatricians of hepatitis B/HIV, as opposed to other groups, will alter in the next decade?	(1) Yes, it will increase (2) Yes, it will decrease (3) No

Commentary

This paper by Buss *et al* demonstrates a poor range of knowledge among paediatric staff about the prevalence of HIV and hepatitis B carriage as well as widespread unsafe clinical practices even when risks were apparently understood. These results are worrying and lead to further questions that should be answered.

- Medical education is failing at an undergraduate and postgraduate level to get important messages across with regards to risk and clinical practice. What is the responsibility of medical schools, individual consultants, and occupational health physicians in ensuring that these simple principles are taught and ensuring that they are implemented?
- Why are 'district sharps policies' so widely disregarded? Are they badly communicated? Are they lost in a deluge of other circulars?
- The behaviour of doctors who have some understanding of risk, but still fail to act appropriately in clinical practice, in many ways reflects the attitudes of the public as a whole in being aware of some individual health risks but then failing, for example, to stop smoking or to lose weight. The reasons behind this should be explored. Is there simply a tradition of neglect of important principles and the norm inherited by each new doctor is passed through the generations of junior staff without critical thought? Is there insufficient time and resources to implement safe practice? What is the effect of fatigue upon incidence of needlestick injuries?

This paper should be discussed in every paediatric department in hospitals and in the community. I fear from the evidence presented here that circulars from occupational health physicians to paediatric staff sink to the bottom of the pile and stay there!

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Bovine IgG and infant colic

The evidence that cows' milk avoidance in some breast feeding mothers prevents the excessive crying which we call infant colic in their babies is impressive.[1] [2] Presumably some component of cows' milk finds its way into breast milk and affects the baby, but what is that component? Bovine β-lactoglobulin and casein are both found in human milk but only in minute amounts about a million times less than in cows' milk. As the frequency of colic is about the same (20%) in breast and bottle fed babies any candidate for offending protein would have more credibility if its concentrations in human and cows' milk were of a similar order. Workers in St Louis, Missouri have looked at bovine IgG (Patrick Clyne and Anthony Kulczycki, *Pediatrics* 1991;87:439–44). Commercial cows' milk based formulas were found to contain bovine IgG at concentrations of the order of 0·5 to 5·0 μg/ml, although one powdered formula had much higher concentrations. Human milk samples commonly contained 0·2 to 1·0 μg/ml of bovine IgG, the highest measured concentration being 8·5 μg/ml.

When milk from the mothers of 29 colicky and 30 non-colicky babies was compared there was a considerable overlap in bovine IgG concentrations but the mean concentration was significantly higher in the group whose babies had colic. No milk sample from a mother of a colicky baby contained less than 0·22 μg/ml of bovine IgG whereas eight of the 30 mothers of babies without colic had milk containing less than that. Repeated samples of milk from the same mother showed fairly constant concentrations. All the babies in the study were exclusively breast fed. Bovine IgG, therefore, seems a credible offender in infantile colic. Interventional studies will be necessary to prove, or disprove, the point.

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Progressive renal toxicity due to ifosfamide

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Abstract

A prospective and follow up study of renal tubular and glomerular function in 11 children receiving ifosfamide treatment was conducted. Each child received between four and 14 courses of ifosfamide, given as a continuous infusion of 3 g/m^2 over 24 hours for two or three days. Evidence of renal toxicity was seen in all patients. There was a treatment related rise in urinary tubular markers (N-acetyl-glucosaminidase and α_1 microglobulin). Recovery was limited, so that by the fourth course of treatment all values remained abnormal. There was an associated treatment related reduction in plasma phosphate concentration. Urinary albumin also showed a treatment related rise, but with fewer abnormal values. Electrophoresis was used to confirm tubular or glomerular patterns. Glomerular toxicity was less severe and occurred in fewer patients. The follow up study showed persistence of tubular damage in all seven patients examined, and there was evidence of glomerular damage in five of the seven children. Children receiving ifosfamide need to be carefully monitored for renal toxicity both during treatment and at follow up.

Before 1980 ifosfamide was precluded from use in children because of its severe renal and bladder toxicity. However, with the introduction of mesna, a uroprotector, ifosfamide has occupied an increasingly important role in solid tumour protocols. While the debate over its efficacy in comparison to cyclophosphamide continues,[1] there are also concerns with regard to its renal toxicity.

There have been a number of case reports of Fanconi's syndrome developing both during treatment,[2] and more frequently, in patients after completion of treatment.[3 4] A cross sectional follow up study has shown combined glomerular and tubular damage presumed to be caused by ifosfamide.[5] Goren *et al* have shown subclinical tubular damage associated with individual ifosfamide treatments, but could find little evidence of progressive nephrotoxicity in children with normal renal function.[6] In order to define more closely the association between ifosfamide and renal toxicity we have performed a combined prospective and follow up study of both tubular and glomerular function in a group of children treated with ifosfamide.

Patients and methods

PATIENTS

The prospective part of this study was performed over a 12 month period at St James's University Hospital. All children being treated with regular courses of ifosfamide were included. Only one child, an 18 month old boy, was excluded because of an inability to collect satisfactory urine samples. A follow up study was subsequently performed on the same group of children.

Eleven children were studied. Their details are given in table 1. Their mean age was 7 years. Five of the children were being treated for relapsed disease. No child was receiving platinum based compounds. All had normal renal function at the start of treatment, as indicated by normal concentrations of plasma creatinine, electrolytes, and phosphate, a normal glomerular filtration rate (GFR) as measured by clearance of diethylenetriamine pentacetic acid (DTPA), and no glycosuria or proteinuria.

Table 1 Patient characteristics

No/sex	*Age (years)*	*Diagnosis*	*Disease status*	*Total dose of ifosfamide (g/m^2)*	*Previous treatment*	*Glomerular filtration rate (ml/min/ 1·73 m^2)*
1/M	3	Neuroblastoma	Relapsed	36	Vincristine, cyclophosphamide, cisplatin, teniposide	125
2/M	3	Rhabdomyosarcoma	Newly diagnosed	85	Nil	126
3/M	5	Wilms' tumour	Relapsed	63	Vincristine, actinomycin	140
4/M	5	Rhabdomyosarcoma	Newly diagnosed	108	Nil	137
5/M	5	Rhabdomyosarcoma	Newly diagnosed	99	Nil	130
6/F	7	PNET*	Relapsed	36	Vincristine, actinomycin, cyclophosphamide	170
7/M	8	Ewing's tumour	Newly diagnosed	129	Nil	145
8/F	8	Wilms' tumour	Relapsed	54	Vincristine, actinomycin, doxorubicin, cyclophosphamide	159
9/F	11	Langerhans' malignancy	Newly diagnosed	96	Nil	137
10/M	12	Schwannoma	Newly diagnosed	63	Nil	133
11/M	12	Rhabdomyosarcoma	Relapsed	63	Vincristine, actinomycin, doxorubicin, cyclophosphamide	134

*PNET=primitive neuroectodermal tumour.

However, patient 2 had evidence of partial left ureteric obstruction caused by his pelvic rhabdomyosarcoma, and patient 3 had a single kidney after resection of his Wilms' tumour. Eight children were studied from course number one, while three were studied from courses number three, four, and five respectively.

Nine patients received ifosfamide as a continous infusion at a dose of 9 g/m^2 given over three days with the same dose of mesna, and accompanied by 3 l/m^2/day of fluid. The hydration and mesna were continued for a further 12 hours after completion of the ifosfamide infusion. Two patients on relapse protocols were started at a lower dose of 6 g/m^2 given over two days. Concomitant treatment included vincristine and actinomycin D or doxorubicin (n=9), or etoposide (n=2). Courses of treatment were given at intervals of three weeks. Dose reductions were performed, where indicated, by protocol instructions (n=4).

INVESTIGATIONS

A sample of urine was collected immediately before each course of ifosfamide and again at completion of the mesna infusion. Samples were collected with azide preservative and frozen until analysed. Pretreatment plasma samples, collected at the same time, were analysed for concentrations of creatinine, electrolytes and phosphate and for alkaline phosphatase activity (American Monitor Parallel Analyzer). Plasma samples were collected after treatment from seven children (patients 2, 3, 4, 6, 8, and 10) on a total of 34 occasions and the phosphate concentration measured.

To assess tubular function we measured urinary N-acetyl-glucosaminidase (NAG), a brush border enzyme, and α_1-microglobulin, a low molecular weight protein. We also measured albumin and transferrin as indicators of more generalised renal damage. Urinary creatinine concentration was measured (Beckman Astra) and proteins expressed as a creatinine ratio. In order to confirm patterns of either glomerular or tubular damage we performed urinary protein electrophoresis.

NAG was measured by colorometric assay (Cortecs Diagnostics), α_1-microglobulin by single radial immunodiffusion, and albumin and transferrin by radioimmunoassay. Urinary protein electrophoresis was performed with sodium dodecyl sulphate polyacrylamide gel (SDS-PAGE) using a PhastSystem as previously described.[7] Normal values for α_1-microglobulin and transferrin were obtained from in house laboratory standards. For NAG, an upper limit of normal of 30 μmol/hour/mmol creatinine was used,[8][9] and for albumin an upper limit of 3 mg/mmol creatinine was used.[10]

FOLLOW UP STUDY

Seven of the original 11 children were alive at a mean of seven months after completion of ifosfamide treatment. A single untimed urine sample was obtained and analysed for concentrations of NAG, α_1-microglobulin, albumin, transferrin and creatinine, and protein electrophoresis was performed. None of the children had received any additional nephrotoxic treatment between completion of the ifosfamide treatment and the time of the follow up study.

Results

PROSPECTIVE STUDY

Sixty seven paired urine samples from before and after treatment were analysed. The results of the urinary markers are summarised in table 2.

NAG

The change in NAG values is represented graphically in fig 1. All children started within

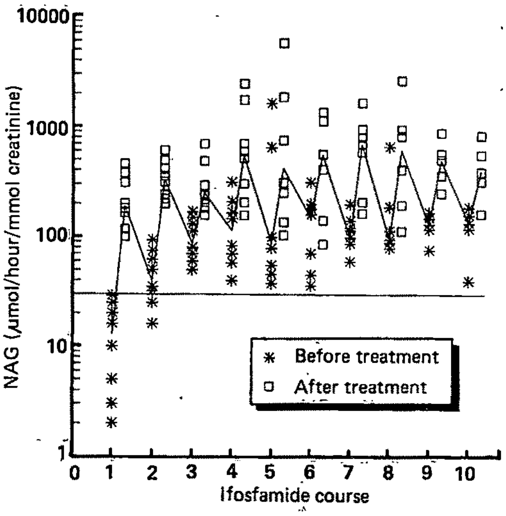

Figure 1 Urinary NAG concentrations before and after treatment. The solid line joins the median values. The horizontal line shows the upper limit of the normal range.

Table 2 Results of urinary markers before and after treatment. Results are median (range)

No of courses of ifosfamide	*No of patients studied*	*NAG (μmol/hour/mmol creatinine)*		*α_1-Microglobulin (mg/mmol creatinine)*		*Albumin (mg/mmol creatinine)*		*Transferrin (μg/mmol creatinine)*	
		Before	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*
1	8	15 (1–20)	192 (100–455)	0·7 (0·5–0·8)	5 (2–30)	0·5 (0·2–2)	2·0 (1·2–14)	15 (8–48)	20 (15–108)
2	8	40 (16–93)	345 (200–610)	0·9 (0·2–16)	12 (3·7–88)	0·5 (0·2–3·4)	2·7 (0·6–18)	15 (4–117)	15 (10–1900)
3	8	88 (50–148)	246 (162–691)	2·0 (0·7–29)	13 (6–100)	1·0 (0·6–2·5)	3·2 (1·4–60)	33 (15–249)	63 (15–2348)
4	7	114 (36–313)	558 (100–455)	1·9 (0·9–27)	12 (4–65)	1·1 (0·4–4·3)	5·3 (1·1–70)	20 (10–357)	51 (12–3691)
5	7	89 (32–1638)	319 (103–5733)	3·5 (1–20)	13 (5–80)	1·3 (0·6–124)	10 (1·7–196)	15 (7–1303)	32 (10–3373)
6	6	169 (30–313)	560 (86–1362)	3·2 (1·8–8)	15 (6–55)	1·3 (0·6–108)	2·0 (1·3–66)	35 (10–4720)	25 (10–645)
7	7	100 (50–200)	708 (166–1663)	3·0 (1–13)	20 (4–35)	1·7 (0·6–18)	2·8 (2·1–15)	78 (21–4469)	40 (7–2536)
8	6	95 (50–190)	617 (113–2630)	3·6 (2·5–8)	22 (10–38)	1·2 (0·5–2·7)	5·3 (4–29)	67 (8–250)	221 (10–1140)
9	5	130 (76–150)	500 (251–1200)	3·3 (1·0–12)	17 (5–31)	4·1 (0·5–9)	6·4 (1·9–39)	71 (40–445)	205 (40–596)
≥10	5	136 (40–160)	388 (164–1125)	4·5 (1·6–13)	16 (10–34)	2·1 (1·1–10)	6·7 (2·6–18)	197 (120–1581)	261 (99–1322)

Normal results: NAG <30 μmol/hour/mmol/creatinine, α_1-microglobulin <0·7 mg/mmol creatinine, albumin <3 mg/mmol creatinine, and transferrin <150 μg/mmol creatinine.

the normal range. Each course of ifosfamide produced a rise in NAG values. Partial recovery occurred between treatments, but was incomplete and became less and less over the first three treatments. By the end of the third course, all values (including values before and after treatment) were outside the normal range. By the fourth course a plateau was reached and all values then remained abnormal, although there was no further progressive rise.

α_1-Microglobulin

An almost identical picture to that described for NAG was found for α_1-microglobulin. The same progressive rise in pretreatment values was seen over the first three courses, with a uniform rise and fall occurring thereafter.

Albumin

Albumin also showed an acute individual treatment related rise (see fig 2). Unlike NAG and α_1-microglobulin there was no progressive increase in pretreatment values, and most remained within the normal range for the duration of the treatment. Abnormal pretreatment values were seen only in two patients. They were patient 2 who had partial ureteric obstruction, and patient 9, where abnormal values were only seen after course number eight. The majority of values after treatment were abnormal, but showed a recovery before the next treatment.

Transferrin

Transferrin showed a variable treatment related effect, with no clear pattern evident. All patients started with normal values. Abnormal values were seen after course number two, and there was a slight upward trend of median values. Extremely high values (greater than 1000 μg/mmol creatinine) were seen in five patients (1, 2, 3, 5, and 9), although there was a large intrapatient variability.

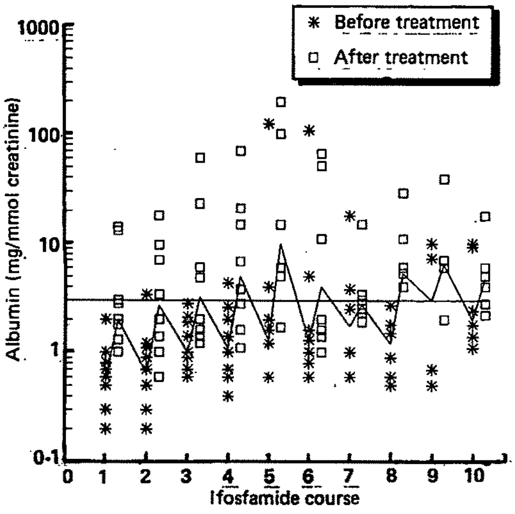

Figure 2 Urinary albumin concentrations before and after treatment. The solid line joins the median values. The horizontal line shows the upper limit of the normal range.

Urine protein electrophoresis

Electrophoretic patterns, with low molecular weight proteins, confirmed the development of generalised tubular proteinuria in all patients. The five patients with the high transferrin concentrations also showed a clear albumin and transferrin band. Generalised glomerular proteinuria with other high molecular bands, was only seen in patients 2 and 9 who had the very high pretreatment albumin concentrations. The majority of high albumin concentrations after treatment were associated with tubular, but not generalised glomerular patterns. Figure 3 shows the development of a generalised tubuloglomerular pattern in patient 2.

Plasma chemistry

All patients had normal plasma creatinine concentrations over the duration of their ifosfamide treatment. All pretreatment phosphate concentrations remained within the normal range, except for patient 2 who had a pretreatment phosphate of 0·82 mmol/l on a single occasion. For the patients where phosphate was measured after treatment, there was a significant treatment related fall, with 40% of these phosphate values being below the lower limit of normal (see table 3). The remaining plasma chemistry was normal.

FOLLOW UP STUDY

Seven children were alive and available for follow up (table 4). All had abnormal NAG and α_1-microglobulin concentrations. Five of the seven also had abnormal albumin and transferrin concentrations. These five patients also had grossly abnormal protein electrophoretic patterns indicating tubuloglomerular damage (see fig 4).

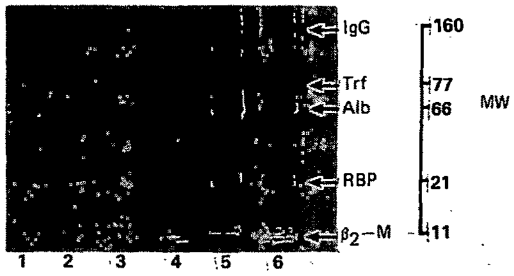

Figure 3 Urinary protein electrophoresis on patient 2. Tracks 1 and 2 are samples taken before and after ifosfamide course 2, tracks 3 and 4 from course 3, and tracks 5 and 6 from course 4. The progressive development of tubuloglomerular pattern is shown. Molecular weight (MW) in kilodaltons is shown on the right. Trf=transferrin, Alb=albumin, RBP=retinol binding protein, and β_2-M=β_2-microglobulin.

Table 3 Plasma phosphate concentrations

	Before treatment	*After treatment*
No of paired samples	34	34
Concentration (mmol/l)*:		
Mean (SD)†	1·39 (0·23)	1·02 (0·24)
Range	0·82–2·16	0·4–1·42

*Lower limit of normal 1·0 mmol/l.
†95% Confidence interval for difference between means was 0·28 to 0·48; $p<0·001$.

Table 4 Follow up study

Patient No	*Time since completion of ifosfamide (months)*	*NAG (μmol/hour/mmol creatinine)*	*α_1-Microglobulin (mg/mmol creatinine)*	*Albumin (mg/mmol creatinine)*	*Transferrin (μg/mmol creatinine)*
2	6	423	41	49	3023
3	14	119	9·5	215	5614
4	6	66	2·3	0·9	93
5	6	50	5	1·6	78
7	7	216	17	25	1608
8	12	69	7	7	721
9	11	90	25	14	819

Normal results: NAG <30 μmol/hour/mmol/creatinine, α_1-microglobulin <0·7 mg/mmol creatinine, albumin <3 mg/mmol creatinine, and transferrin <150 μg/mmol creatinine.

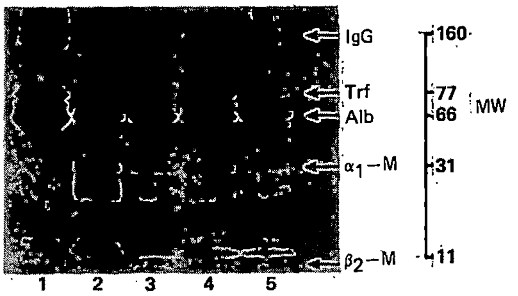

Figure 4 Follow up samples from patients 3 (track 1), 2 (2), 7 (3), 8 (4), and 9 (5) respectively. Sample for patient 3 was diluted 1:2. All five patients have a generalised tubuloglomerular pattern. Molecular weight (MW) in kilodaltons is shown on the right. Trf=transferin, Alb=albumin, α_1-M=α_1-microglobulin, and β_2-M=β_2-microglobulin.

Discussion

This study documents the pattern of tubular and glomerular damage occurring in patients receiving ifosfamide.

A progressive increase in pretreatment renal tubular markers was seen in all patients over the first three to four courses of treatment. Thereafter a uniform zigzag pattern was maintained. Urine protein electrophoresis confirmed the presence of generalised tubular proteinuria, which occurred in all patients. After the fourth course, recovery to normal concentrations was not seen. These findings are in contrast to those described by Goren *et al*, who found persistently abnormal pretreatment values in only one out of 18 patients.[6] This may partly be due to the older age range of the patients studied by Goren *et al.* Measurement of plasma phosphate confirmed that for most of the children this damage was subclinical. Each ifosfamide treatment was usually associated with a fall in plasma phosphate, however, and in 40% of cases the phosphate concentration after treatment was abnormally low.

Albumin is classed as a glomerular protein. It is the smallest of the 'glomerular' proteins with a molecular weight of 66 kilodaltons, and its excretion rate is therefore affected by damage to the basement membrane. Like the tubular markers, albumin was also directly affected by ifosfamide, with increased concentrations seen after each ifosfamide treatment. Most pretreatment values remained within the normal range and there was no noticeable progressive rise.

Transferrin has similar physical characteristics to albumin, with a molecular weight of 77 kilodaltons. Transferrin is a complex molecule and is involved in a number of metabolic processes.[11] Diferric transferrin is specifically concentrated by damaged tissue and actively proliferating cells. In the former it is associated with the superoxide dismutase reaction and in the latter with ribonucleotide reductase. In damaged renal tissue, active concentration of diferric transferrin will cause an increase in the intracellular concentration of apotransferrin which in turn will cause an increase passage of the molecule through the glomerulus. There was no uniform increase in urinary transferrin related to individual course of treatment. Each patient had a variable pattern with the highest values often occurring in the pretreatment sample. For most of the patients with appreciably raised transferrins, the urine protein electrophoresis did not show generalised glomerular damage. These facts indicate that transferrin was being handled differently to albumin and probably reflect an association with renal damage repair processes.

Generalised glomerular damage, as indicated by electrophoresis, occurred in only two patients during the prospective study. In one the presence of partial ureteric obstruction was a predisposing factor. Glomerular damage is therefore less noticeable and less acute than tubular damage. The presence of abnormal transferrin and abnormal albumin values after treatment in the majority of patients may point to a slowly accumulating glomerular damage, and thereby contribute to the striking follow up findings.

It would be helpful if known risk factors together with the use of urinary markers could predict the development of early and/or clinically significant toxicity. Underlying renal abnormalities are a known risk factor, and there is some evidence from the literature that young age may also be important.[5] Though the development of microalbuminuria or even generalised proteinuria is clearly abnormal, the significance of a single finding may not be immediately apparent. It should nevertheless provide a warning for further evaluation.

This follow up study confirms the presence of tubular and glomerular damage found by Skinner *et al.* All patients showed abnormal tubular markers. It is therefore not surprising that patients may present late with hypophosphataemic rickets and Fanconi's syndrome. While all these patients are exposed to a number of potentially nephrotoxic drugs during their prolonged course of treatment, it appears from this study that ifosfamide is a significant contributory factor to persisting tubular damage.

The presence of generalised glomerular damage in five out of seven patients at follow up is worrying in that it suggests the possibility of progressive glomeruler damage in some patients. Further follow up studies will be needed to establish if any recovery occurs with time. It is clear that all patients receiving ifosfamide need to be closely monitored for renal toxicity, not only during treatment, but also at follow up. In addition, these findings need to be taken into account in the debate on the therapeutic role of ifosfamide.

We wish to thank the nursing staff on ward 15 for their help in collection of specimens.

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. . . . and carrying colicky babies

A study from McGill University, Montreal, published in 1986 showed that crying was significantly less in mothers of normal babies who were asked to increase the time for which they carried their babies when they were not crying.[1] So if it works for normal babies why not for colicky babies? Which begs the question: are colicky babies different or are they simply the upper end of the normal range as regards crying?

The same workers in Montreal (Ronald G Barr and colleagues, *Pediatrics* 1991;87:623–30) have carried out a randomised controlled trial of extra carrying in infant colic. They defined colic as excessive crying in a young baby which was both presented as a problem by the mother and seen as a problem by the doctor. Seventy eight mother-baby pairs were recruited of whom 12 did not complete the study. All the babies were less than 29 days old on entry to the study. Of the 66 who completed the study 35 were assigned to 'standard treatment'. That is the mothers were advised to respond to their babies crying by comforting them, to breast feed them if appropriate, to give them smaller more frequent feeds if bottle fed, to place the baby in a seat near to mother, and to use distractions such as music or a car ride. The other 31 were given the same advice but in addition were advised to carry their babies for at least an extra three hours a day.

There was no significant difference in crying or fussing behaviour between the two groups. This result needs to be interpreted with caution, however. Both groups of babies were given a lot of attention by their parents and at entry to this study the mothers were already carrying their babies as much as did the mothers in the previous study who increased their carrying (just over four hours each day).[1] Perhaps four hours a day is enough and carrying more than that produces no benefit. A previous study has shown parent counselling to be more effective than cows' milk avoidance.[2]

A sensible approach seems to be to advise parents to be responsive to their babies and to carry them up to four hours a day. If such measures don't work then cows' milk avoidance by either the baby or the breast feeding mother should be considered.

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Colorectal neoplasia in juvenile polyposis or juvenile polyps

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Abstract

Juvenile (retention) polyps are usually solitary lesions in the colorectum but may be multiple in juvenile polyposis. The association between juvenile polyps and colorectal neoplasia is controversial. We present three patients with juvenile polyposis who had colorectal adenomas or adenomatous epithelium in juvenile polyps at ages 3, 4, and 7 years. In a retrospective study of 57 additional patients with one or more juvenile polyps, 10 patients (18%) had colorectal neoplasia including three with adenocarcinoma, two with tubular adenoma, and six with adenomatous epithelium in a juvenile polyp (one had both adenomatous epithelium and an adenocarcinoma). Nine of these 10 patients had juvenile polyposis defined by the presence of at least three juvenile polyps; and eight of the nine had a family history of juvenile polyps. Colorectal neoplasia occurred at young age (mean (SEM) 37 (5) years).

Our findings suggest that patients with juvenile polyps who have three or more juvenile polyps or a family history of juvenile polyps should undergo surveillance for colorectal neoplasia.

The term 'juvenile polyp' was used by Horrilleno in 1957 to designate histologically distinctive colorectal polyps that usually occurred as solitary lesions in children.[1] However, other authors reported that multiple juvenile polyps representing juvenile polyposis can occur, not only throughout the colorectum[2–9] but also occasionally in the small bowel and stomach.[10–12] In addition, families with juvenile polyposis in several members have been reported. Analysis of a limited number of such juvenile polyposis families revealed variability among pedigrees in location of gastrointestinal tract polyps and heritability of this condition.[13 14]

Juvenile (retention) polyps are generally thought to be hamartomatous lesions with little malignant potential. Consequently, a conservative approach toward treatment, involving only removal of the polyp, has been taken. Some reports, however, have documented the occurrence of colorectal adenomas and carcinomas in patients with single juvenile polyps as well as in those with juvenile polyposis.[3 4 12 15–24] Thus the nature of the association between juvenile polyps and colorectal neoplasia is controversial.

Between 1984 and 1990, four young children (ages 4–7 years) with juvenile polyposis were evaluated at our institution. Three of these four children were found to have a colorectal adenoma or adenomatous epithelium in a juvenile polyp. Therefore, to assess the frequency of colorectal neoplasia and identify features associated with its occurrence, patients with one or more juvenile polyps at The Johns Hopkins Hospital from 1972 through 1980 were reviewed.

Methods

PROSPECTIVE STUDY

Four children with juvenile polyposis evaluated at The Johns Hopkins Hospital from 1984 through 1990 were identified prospectively. The computerised surgical pathology diagnosis file in the department of pathology was searched systematically, but no additional cases were found in this time period. The clinical records and pathological material of the four cases were reviewed.

RETROSPECTIVE STUDY

We investigated the association between juvenile polyps and colorectal neoplasia by retrospective review of all juvenile polyp cases identified by searching the surgical pathology files and The Johns Hopkins Bowel Tumor Registry for the nine year period of 1972 through 1980. The histopathological sections of the polyps were reviewed by a gastrointestinal pathologist (SEK/SRH) to confirm the diagnosis using established criteria.[35] Fifty seven patients with one or more juvenile polyps were identified. All polyps were located in the colorectum. Each patient's medical records and a mailed questionnaire to patients and their physicians were also evaluated.

Patients were distinguished as familial or non-familial cases on the basis of family history of juvenile polyp(s). Family history was considered positive for juvenile polyp(s) if at least one first degree relative was affected as verified by physician contact. Patients were considered to have juvenile polyposis if they had three or more colorectal juvenile polyps. Colorectal neoplasia was considered to be present if the patient had an adenocarcinoma, an adenoma, or adenomatous epithelium in a juvenile polyp in the large bowel. All cases with colorectal neoplasia were verified through histopathological review by both gastrointestinal pathologists (SEK and SRH). Polyps of three familial and one non-familial patient judged indefinite for adenomatous epithelium were regarded as negative in the analysis of results.

In addition to the 57 cases that fulfilled our criteria and formed the present study popula-

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tion, 11 patients identified in the same period with a polyp histologically consistent with juvenile polyp were excluded. These cases had a history of inflammatory bowel disease (n=9) or polyps occurring at an anastomotic site from previous surgery (n=2) and were judged to have inflammatory polyps rather than juvenile polyps.

Our findings were also compared with literature reports of patients with juvenile polyps. Literature search from 1966 to 1990 was performed through MEDLINE, accessed via the BRS Colleague Search Service.[36]

Results

PROSPECTIVE STUDY

Four children with juvenile polyposis were seen at The Johns Hopkins Hospital between 1984 and 1990. The cases are summarised in table 1 and illustrated in fig 1. Rectal bleeding was the presenting complaint in each case. The ages at diagnosis of juvenile polyposis by colonoscopy with biopsy or polypectomy were 3, 4, 6, and 7 years old. All patients were female. There was no family history of juvenile polyps, juvenile polyposis, or colorectal cancer in any of these cases. Adenomatous epithelium was present in

Table 1 Juvenile polyposis cases in 1984–90

	Case A	*Case B*	*Case C*	*Case D*
Age at diagnosis of juvenile polyposis (years)	3	4	6	7
Race: white (W)/black (B) and sex	WF	BF	WF	WF
Family history of juvenile polyposis	No	No	No	No
Age at diagnosis of colorectal neoplasia (years)	3	4	—	7
Family history of colorectal cancer	No	No	No	No
Type of neoplasia	Adenomatous epithelium in juvenile polyp(s)	Adenomatous epithelium in juvenile polyp(s), tubulovillous adenoma	None	Tubulovillous adenomas
Type of specimen	Polypectomy	Polypectomy, colectomy	Polypectomy	Colectomy
Neoplasia sites in colon	Rectum, transverse	Rectum, sigmoid, ascending	None	Rectum, transverse

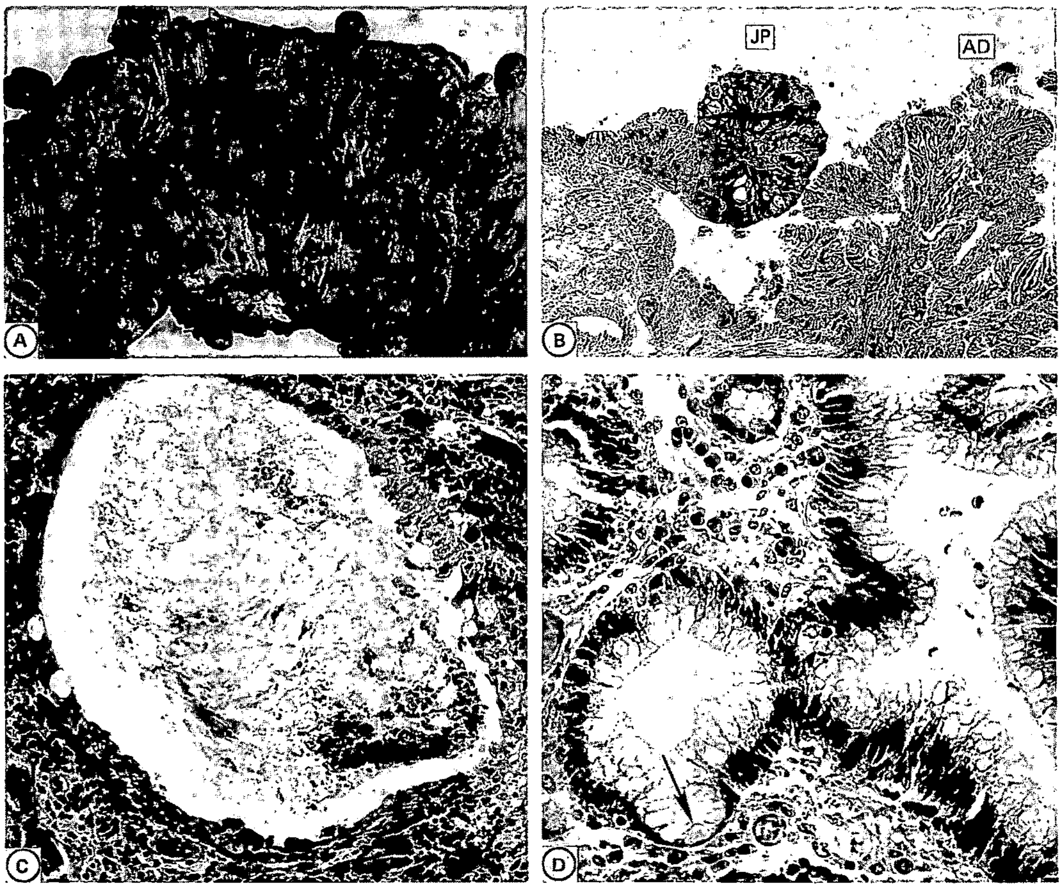

Figure 1 Colectomy specimen from case B in table 1. (A) Gross photograph shows numerous polyps of varying sizes and configurations (×0·6). (B) Photomicrograph of juvenile polyp (JP) and separate tubulovillous adenoma (AD) in the ascending colon. The frond like appearance of the adenoma is strikingly different from the ovoid juvenile polyp (haematoxylin and eosin, ×45). (C) High power photomicrograph of juvenile polyp in (B). The dilated gland contains fibrinoinflammatory exudate and has flattended epithelium. The surrounding stroma consists of inflamed granulation tissue. No adenomatous epithelium is present (haematoxylin and eosin, ×190). (D) High power photomicrograph of tubulovillous adenoma in (B). The epithelium is hypercellular with stratified, spindle shaped nuclei. Proliferated paneth cells (arrow) are present in the neoplastic epithelium (haematoxylin and eosin, ×380).

juvenile polyps removed by polypectomy from two children at ages 3 and 4 years old (cases A and B in table 1). Two children underwent colectomy for persistent bleeding (cases B and D). In case B, who had adenomatous epithelium in juvenile polyps at age 4, a tubulovillous adenoma which had not been identified by two previous colonoscopies was present in the colectomy specimen at age 7 (fig 1). In the other child (case D) two adenomas that had not been detected by a previous colonoscopy with multiple biopsies were identified in the colectomy specimen at age 7.

RETROSPECTIVE STUDY

The demographics of the retrospective study group of 57 patients are shown in table 2. A family history of juvenile polyps in a first degree relative was present in 20 of 57 patients representing six different families. Eight of the 20 (40%) patients in the familial group had colorectal neoplasia (table 3). This included adenocarcinoma (n=2), tubular adenoma separate from juvenile polyps (n=2), and adenomatous epithelium in juvenile polyps (n=4). Interestingly, seven of these eight (88%) patients with colorectal neoplasia were males. In contrast to the familial group, only two of 37 (5%) patients without family history of juvenile polyps had colonic neoplasia ($p<0{\cdot}01$): both had adenomatous epithelium in juvenile polyps and one had a separate adenocarcinoma of the rectum.

In addition to family history, the finding of multiple juvenile polyps was associated with colorectal neoplasia. Colorectal neoplasia was found in nine of 19 patients with three or more colorectal juvenile polyps, as compared with only one of 28 patients with one or two polyps ($p<0{\cdot}01$) (fig 2). When analysed, family history and multiple juvenile polyps were interrelated variables: eight patients had both. Importantly, one of two non-familial patients with colorectal neoplasia had more than 40 juvenile polyps in the large intestine and can be considered a new mutation of juvenile polyposis (arrow in fig 2; case 9 in table 3). This patient had both rectal adenocarcinoma and adenomatous epithelium in multiple juvenile polyps. The second patient had adenomatous epithelium in a solitary juvenile polyp. These results suggest that juvenile polyposis can be established by three or more colorectal juvenile polyps, especially if there is a family history of a juvenile polyp.

Table 2 Characteristics of retrospective study population with juvenile polyps

	Familial (n=20)*	*Non-familial (n=37)*	*Combined (n=57)*
No (%) males	11 (55)	20 (54)	31 (54)
Mean (SEM) age at diagnosis of juvenile polyps (years)	23 (4)	22 (3)	22 (2)
Range	3–58	2–58	2–58
No (%) with colorectal neoplasia	8 (40)	2 (5)	10 (18)
Mean (SEM) age at colorectal neoplasia (years)	37 (5)	38 (15)	37 (5)
Range	6–58	23–52	6–58

*History of juvenile polyps in a first degree relative.
†$p<0{\cdot}01$ compared with non-familial group.

The mean (SEM) age of diagnosis of colonic neoplasia was similar in the familial and non-familial (37 (5) years, range 6–58; and 38 (15), range 23–52, respectively). Neoplastic changes were diagnosed at the time of initial juvenile polyp diagnosis in four patients and during follow up in six patients. The mean length of

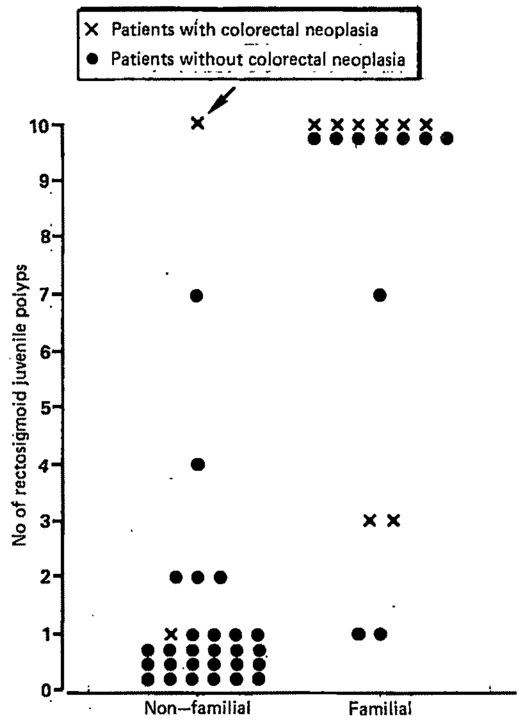

Figure 2 Occurrence of colorectal neoplasia in patients with juvenile polyp(s) in relation to family history of juvenile polyp and number of juvenile polyps.

Table 3 Characteristics of colorectal neoplasia observed in retrospective study population

Case No	*Family No*	*Age at neoplasia diagnosis*	*Sex*	*Multiple juvenile polyps (≥3)*	*Type/site of colorectum neoplasia*
Familial					
1	1	6	M	Yes	Adenomatous epithelium in juvenile polyp(s)
2	3	27	F	Yes	Tubular adenoma separate from juvenile polyp(s)
3	3	56	M	Yes	Adenocarcinoma of colon
4	4	42	M	Yes	Tubular adenoma separate from juvenile polyp(s)
5	4	58	M	Yes	Adenocarcinoma of rectum
6	5	42	M	Yes	Adenomatous epithelium in juvenile polyp(s)
7	5	38	M	Yes	Adenomatous epithelium in juvenile polyp(s)
8	6	26	M	Yes	Adenomatous epithelium in juvenile polyp(s)
Non-familial					
9	—	23	F	Yes	Adenomatous epithelium in juvenile polyp(s) and separate adenocarcinoma of rectum
10	—	52	M	No	Adenomatous epithelium in juvenile polyp(s)

Table 4 Previous reports of colorectal neoplasia in patients with juvenile polyp(s)

Report (reference Nos)	*No of cases*	*Age (years)*		*Sex (M/ total, % M)*	*Family history of juvenile polyps (%)*	*Type of colorectal neoplasia*
		Mean (SEM)	*Range*			
Solitary juvenile polyp:						
16–21	8	24 (9)	1·5–67	4/7* (57)	2/8 (25)	Carcinoma in juvenile polyp (n=1), adenoma epithelium in juvenile polyp (n=3), carcinoma and adenoma in juvenile polyp (n=1), separate carcinoma (n=1), separate adenoma (n=2)
Multiple juvenile polyps (≥3):						
3, 4, 12, 15, 22, 23, 25–34, 40, 42	39	27 (2)	6–52	25/38* (66)	15/39 (38)	Carcinoma in juvenile polyp(s) (n=1), adenoma epithelium in juvenile polyp(s) (n=13), carcinoma and adenoma in juvenile polyp(s) (n=3), carcinoma unknown site (n=16), separate adenoma (n=6)

*Sex not specified in one case.

follow up was 5·1 (1·6) years. When considered by pedigree all six families with familial juvenile polyposis had at least one member with colorectal neoplasia (adenocarcinoma or adenoma). However, a family history of colorectal neoplasia was noted in only two of 37 families in the non-familial group ($p<0.001$ compared with familial group).

Discussion

Juvenile polyps of the colorectum have generally been considered benign hamartomas.[16 37–39] Controversy concerning the malignant potential in patients with these polyps has existed for decades, however,[1] because investigators have reported the occurrence of colorectal adenoma and carcinoma in patients with solitary as well as multiple colonic juvenile polyps (table 4).[3 4 12 15–24 26–34 40]

The occurrence of colorectal adenomas or adenomatous epithelium in three young children with juvenile polyposis at our institution prompted us to review the association of colorectal neoplasia with juvenile polyps. There was a striking occurrence of colorectal neoplasia in juvenile polyp patients with either a family history of juvenile polyps (40%) or with three or more rectosigmoid juvenile polyps (47%): eight of 10 patients with neoplasia had both features. The association of colorectal neoplasia with juvenile polyposis despite the absence of family history is highlighted by case 9 (marked by arrow in fig 2; table 3). Although this patient had no family history of juvenile polyps, at age 23 years she had multiple juvenile polyps with adenomatous epithelium and a rectal adenocarcinoma.[41] Similar to the young children prompting this investigation, such patients may well represent new mutations for the juvenile polyposis gene, explaining the absence of family history.

The literature supports our conclusion that juvenile polyposis is associated with colorectal neoplasia. Thirty eight of 46 reported cases of colorectal neoplasm and juvenile polyps occurred in patients with multiple juvenile polyps (table 4). Also, in a recent study Jass *et al* noted that 18 of 80 (23%) juvenile polyposis patients (those with more than five juvenile polyps) developed colorectal cancer.[15] Interestingly, 83% of these patients were male, and in our study seven of eight (88%) patients with colorectal neoplasia and a family history of juvenile polyps were male. On the other hand, our three prospectively observed cases without a family history were female (cases A, B, D in table 1) as was the non-familial case in the retrospective study (case 9 in table 3, arrow in fig 2).

On the basis of our study and literature review, we recommend that, when possible, juvenile polyp patients with multiple juvenile polyps (three or more) or a family history of juvenile polyps should have a complete colonoscopic examination. Periodic surveillance by colonoscopy with multiple random biopsies of both polyps and flat mucosa every several years seems appropriate for these patients. Also, screening of first degree relatives is prudent because of the difficulty in recognising asymptomatic affected individuals. At times colonoscopic surveillance may be difficult especially in juvenile polyposis patients with numerous polyps. Colectomy is a consideration in these individuals because neoplasia may not be sampled by biopsies and polypectomies, as illustrated by case D in table 1. Presently, there do not appear to be sufficient data from juvenile polyposis patients to justify prophylactic colectomy solely for the risk of colorectal carcinoma, as is done in adenomatous polyposis. However, in the presence of any other indications such as persistent rectal bleeding, colectomy is appropriate.

Although much less frequently reported, patients with solitary juvenile polyps and no family history have developed colorectal neoplasia. Our one case of this type was a 52 year old man (case 10, table 3). Literature review revealed eight cases of infants and children developing neoplasia in solitary juvenile polyps (table 4). Therefore, solitary juvenile polyps should usually be removed, even if asymptomatic, because of the small but definite neoplastic potential.

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Sleeping position and rectal temperature

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Abstract

The effects of sleeping position upon body temperature were assessed by continuous monitoring of rectal temperature in 137 babies sleeping at home under conditions chosen by their parents. There were three groups of subjects: (1) normal babies aged 12–22 weeks whose temperature rhythms were developed, (2) normal babies aged 6–12 weeks who were developing their night time temperature rhythms, and (3) babies the night after diphtheria, pertussis, and tetanus immunisation, whose temperature rhythms were disturbed. Sleeping in the prone position was not associated with higher rectal temperatures at any time of night in young babies, nor did it exaggerate the disturbance of rectal temperature rhythm after immunisation. In older normal babies the prone position did not disturb rectal temperature in the first part of the night, though prone sleepers warmed a little faster prior to waking, especially in warm conditions. Prone sleepers were, however, born earlier in gestation and tended to be of lower birth weight. Normal babies can therefore thermoregulate effectively whatever their sleeping posture, even in warm conditions, though the prone position may make it slightly more difficult to lose heat. It is difficult to see how the prone position, even interacting with warm conditions, could induce lethal hyperthermia in otherwise normal babies. Perhaps the prone position is associated with other risk factors for sudden infant death syndrome.

A number of reports have suggested that sleeping in the prone position may be associated with an increased risk of cot death.[1–3] It has been suggested that the prone position increases the risk of overheating in the cot, particularly if babies are covered with a large amount of thermal insulation and sleeping in warm rooms.[3]

By 3 months of age babies have developed a consistent night time rhythm of deep body temperature, which seems to be maintained irrespective of environmental conditions.[4] There have been no reports of the effects of sleeping position on this rhythm. It may be that babies sleeping prone show alterations of their temperature patterns, particularly in warm conditions, supporting the suggestion that it is difficult for them to lose heat.

Even if normal babies do not show altered temperature rhythms when prone, it might be that other factors tending to raise body temperature, such as a developing minor infection, might be more potent when sleeping in that position. We have yet to find a way of monitoring sufficient numbers of babies in the very early stages of minor infection to test this hypothesis directly but we do have a model which may resemble the changes, namely the disturbance of temperature rhythm which follows diphtheria, pertussis, and tetanus (DPT) immunisation.[5] The night after this immunisation rectal temperature does not fall in the usual way and remains about that expected during the day in most babies, though the extent of the elevation over the normal night time value varies considerably from individual to individual. We have seen a similar pattern in a few babies, who developed an observable minor infection a day or two after temperature recording, even though they were not apparently ill at the time of recording.

In this study, therefore, we compared the night time rectal temperature patterns of normal babies of different ages sleeping in different positions in their cots at home. As parents choose a wide variety of clothing, wrapping, and room temperatures we were able to examine the effects of warm and cool conditions. We have also examined the effects of sleeping position upon the changes in rectal temperature after immunisation.

Methods

In the course of our studies on the development of temperature rhythms,[6] and the effects of immunisation,[5] we have routinely recorded the sleeping position of babies. This was determined by direct observation by a trained health visitor. We have collated data from these studies in this paper, incorporating recordings from a total of 137 babies.

In all cases subjects were recruited by liaison with local general practitioners and health visitors. Basic perinatal data were collected before making arrangements to monitor body temperature at home over one or more nights at various ages.

On each recording night the baby was visited at home in the early evening, weighed naked, and temperature probes were attached. One soft probe, inserted 5 cm from the anal margin, measured rectal temperature, and other probes measured skin surface temperature on the head and either the abdomen or shin. Only rectal temperature data will be discussed here. A fourth probe measured the ambient temperature at the cot side. All probes were connected to a Grant Squirrell data logger set to sample at one minute intervals throughout the night. These techniques have been demonstrated to be both effective and safe,[4] and full ethical committee approval was obtained for all the studies from which data have been abstracted for this paper.

At bedtime, sleeping position was noted by the health visitor. 'Prone' was defined as having the ventral surface of the trunk in symmetrical contact with the mattress cover, irrespective of the head position. 'Lateral' was having either the left or right side of the trunk in contact with the mattress covering and the humerus of both arms flexed at the shoulder joint. 'Supine' was having the dorsal surface of the trunk in symmetrical contact with the mattress cover. In a number of cases sleeping position was monitored for the first six hours of the night by infrared thermographic imaging. Some babies moved from the lateral to supine position and we have merged data from these two positions and compared it with that for prone babies; these babies have not been observed to move to the lateral or supine position (at least, not babies of the age range considered here).

Parents were asked to keep a diary of events such as feeds, nappy changes, periods of waking, etc, throughout the period of recording. Note was also made of the items of clothing and wrapping used by parents, so that a thermal insulation or 'tog value' could be calculated from data provided by the Shirley Institute, Manchester.

After each recording data were downloaded from the loggers to a computer and scrutinised for technical problems such as loss of probes. Only unblemished data were analysed further. Mean rectal temperatures, together with their standard errors, were calculated at half hour intervals, from one hour before bedtime until eight hours after bedtime, for various groups of babies sleeping either prone or supine/lateral. Statistical comparisons were made by Student's *t* test.

Results

SUBJECTS

Data were collated from body temperature recordings of three groups of babies sleeping at home: (1) 79 normal babies aged 12–22 weeks, (2) 26 normal babies aged 6–12 weeks, and (3) 33 normal babies sleeping at home the night after first DPT immunisation. The unimmunised babies were separated into two age groups because temperature rhythms are not completely developed until 12 weeks of age.[4] Of the 136 babies studied, 126 were born at 36 weeks of gestation or later. The social class distribution of the families resembled that of the Leicester population as a whole.

(1) Normal babies aged 12–22 weeks

Within this group 50 (63%) of the babies were in the prone position at bedtime and 29 (37%) either lateral or supine. The prone babies had a mean (SEM) age of 16·00 (0·36) weeks, were covered with 12·34 (0·53) tog units of insulation (range 3·4–22·5), and slept in rooms where the minimum temperature was 16·62 (0·42)°C and the maximum temperature 20·23 (0·45)°C. Babies sleeping in the lateral or supine position were 16·00 (0·51) weeks of age, were covered with 13·23 (0·90) tog units of thermal insulation (range 6·2–20·65), and slept in rooms where the minimum temperature was 16·89 (0·44)°C and the maximum temperature 21·34 (0·42)°C (table).

There were no significant differences in age, tog value, or room temperature between babies sleeping prone and those sleeping supine or lateral. Babies sleeping prone were, however, born significantly earlier in gestation (mean gestation for prone sleepers was 38·47 (0·45) weeks, for lateral/supine sleepers 39·51 (0·31), $p<0·05$ unpaired *t* test).

Figure 1 shows the night time rectal temperatures of babies sleeping in different positions. There were no significant differences at any time between babies sleeping prone and those sleeping supine or lateral. The body temperature of babies sleeping prone was not signifi-

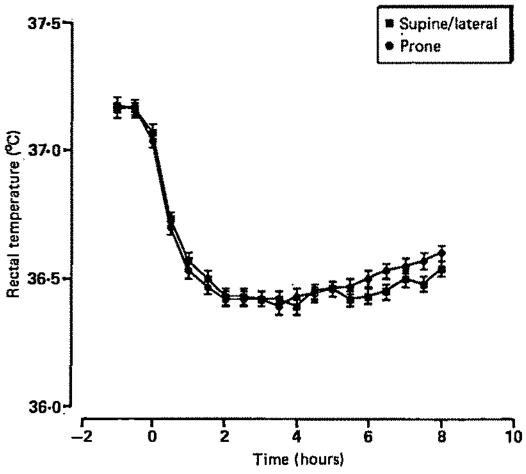

Figure 1 The rectal temperature of babies aged 12–22 weeks sleeping in the prone or supine/lateral position at night. Points show mean (SEM) of observations from 50 babies sleeping prone and 29 sleeping supine/lateral. Times are normalised to bedtime.

Details of the babies in the three groups. Results are mean (SEM)

	(1) Normal babies aged 12–22 weeks		*(2) Normal babies aged 6–12 weeks*		*(3) Normal babies after first DPT immunisation*	
	Prone (n=50)	*Not prone (n=29)*	*Prone (n=11)*	*Not prone (n=15)*	*Prone (n=13)*	*Not prone (n=19)*
Age (weeks)	16·00 (0·36)	16·00 (0·51)	9·54 (0·62)	9·66 (0·31)	14·3 (0·40)	14·26 (0·20)
Tog value	12·34 (0·53)	13·23 (0·90)	8·65 (0·38)*	13·52 (0·32)	10·58 (0·92)	11·03 (0·95)
Range	3·40–22·50	6·20–20·65	5·70–13·90	6·20–18·60	4·90–14·70	5·10–15·70
Minimum room temperature (°C)	16·62 (0·42)	16·89 (0·44)	18·59 (0·33)*	16·88 (0·58)	18·24 (0·64)	18·25 (0·75)
Maximum room temperature (°C)	20·23 (0·45)	21·34 (0·42)	22·56 (0·57)	21·83 (0·42)	21·68 (0·95)	21·5 (0·85)
Gestational age (weeks)	38·47 (0·45)	39·51 (0·31)*	37·25 (0·80)	39·42 (0·53)*	39·30 (0·62)	39·50 (0·38)

*Significant differences ($p<0·05$) between prone and not prone.

cantly different at bedtime, nor did it fall significantly less, or rise significantly more later in the night. There was, however, a trend for prone babies to warm a little faster towards the end of the night. This is more obvious if data are collated only for the more heavily wrapped babies in warmer rooms. The rectal temperature of babies sleeping prone, and covered with more than 15 tog units in rooms above 18°C, is significantly ($p<0·05$) higher than that of babies sleeping supine/lateral from six hours after bedtime (fig 2).

The difference in rectal temperature late in the night was not associated with earlier waking in infants sleeping prone. There was no significant difference in the interval from bedtime to first disturbing the parents between prone and lateral/supine sleepers.

(2) *Normal babies aged 6–12 weeks*

In this group 11 (42%) were in the prone position at bedtime and 15 (58%) either lateral or supine, with lateral predominating. The prone babies had a mean (SEM) age of 9·54 (0·62) weeks, were covered with 8·65 (0·88) tog units of insulation, and slept in rooms where the minimum temperature was 18·59 (0·33)°C and the maximum temperature 22·56 (0·57)°C. Babies sleeping lateral or supine were 9·66 (0·31) weeks old, were covered with 13·52 (0·32) tog units of insulation, and slept in rooms where the minimum temperature was 16·88 (0·58°C and the maximum temperature 21·83 (0·42)°C (table).

The prone sleepers were covered with significantly less insulation ($p<0·01$, *t* test with 24 df) but were in significantly warmer rooms ($p<0·01$, *t* test with 24 df on minimum temperatures). As with the older group the prone babies were born significantly earlier in gestation (gestation 37·25 (0·80) weeks for prone babies; 39·42 (0·53) for supine/lateral, $p<0·01$ *t* test with 24 df).

Figure 3 shows the rectal temperatures over the night for young babies sleeping in the prone or supine/lateral positions. There were no significant differences between the groups at any time. The body temperature of babies sleeping prone was not significantly different at bedtime, nor did it fall significantly less, or rise significantly more later in the night.

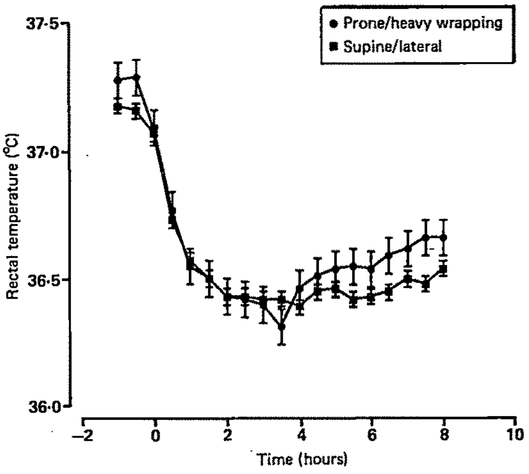

Figure 2 The rectal temperature of babies aged 12–22 weeks sleeping in the prone position covered with more than 15 tog units in rooms where the average temperature exceeded 18°C, compared with that of babies sleeping supine. Points show mean (SEM) of observations from 11 babies sleeping prone and 29 sleeping supine or lateral. Times are normalised to bedtime.

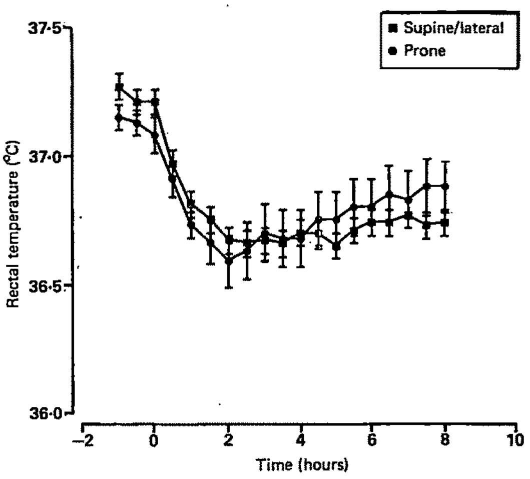

Figure 3 The rectal temperatures of babies aged 6–12 weeks sleeping in the prone or supine/lateral position at night. Points show mean (SEM) of observations from 11 babies sleeping prone and 15 sleeping either supine or lateral. Times are normalised to bedtime.

(3) *Normal babies the night after first DPT immunisation*

Of the 32 babies in this group 13 (41%) were prone and 19 (59%) supine/lateral at bedtime. The prone babies had a mean (SEM) age of 14·3 (0·4) weeks and those supine or lateral averaged 14·26 (0·2) weeks old. Prone babies were covered with 10·58 (0·92) tog units of insulation in rooms where the minimum temperature was 18·24 (0·64)°C and the maximum temperature 21·68 (0·95)°C. Babies sleeping in the supine/lateral position were covered with 11·03 (0·95) tog units of insulation in rooms where the minimum temperature was 18·25 (0·75)°C and the maximum temperature 21·5 (0·85)°C (table).

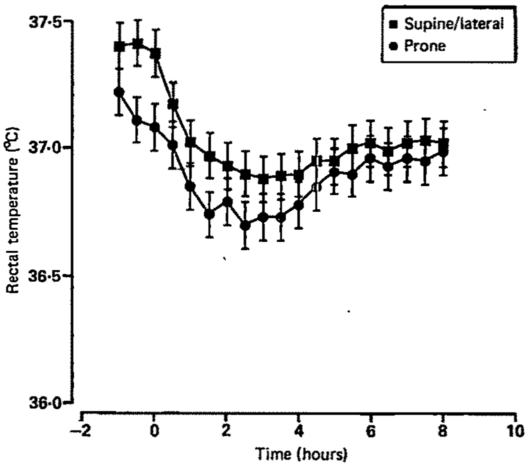

Figure 4 The rectal temperature of babies sleeping in the prone or supine/lateral position the night after their first DPT immunisation. Points show mean (SEM) from 13 babies sleeping prone and 19 sleeping supine or lateral. Times are normalised to bedtime.

There were no significant differences in age, thermal insulation, maximum or minimum temperatures between babies sleeping in different positions. The prone babies tended to be born earlier in gestation, though this trend was not significant.

Figure 4 shows the rectal temperature of babies sleeping prone or supine/lateral the night after the first DPT immunisation. There were no significant differences at any time of the night. The body temperature of babies sleeping prone was not significantly different at bedtime, nor did it fall significantly less, or rise significantly more later in the night.

Discussion

Combining the groups studied here we find that 54% of babies were prone at bedtime. This is a figure that compares with that in an earlier report,[3] though in that part of our sample recorded after mid 1989 there is a smaller proportion of prone sleepers, suggesting that parental behaviour may be changing. Although prone babies did not sleep in different thermal conditions, they were born significantly earlier in gestation.

By 12 weeks of age babies have developed a predictable rhythm of night time temperature change.[6] Rectal temperature falls after bedtime, stabilises around 36·4°C for a few hours, then rises gradually before waking. During the falling phase, and while the temperature is stable, there are no observable effects of thermal environment on rectal temperature.[4] It is clear that the babies are thermoregulating effectively, though most are sleeping in environments where we would expect it to be difficult to lose heat.[7]

There is no effect of sleeping position upon the the first two phases of night time rectal temperature change. Early in the night the prone position is not associated with raised rectal temperature, though of course it may be that maintenance of a stable temperature requires greater changes in vasomotor activity or sweating in that position. Later in the night, however, prone babies do warm a little faster, a trend that is exaggerated in the babies who are well wrapped in warm rooms. These observations support the speculation that prone babies may lose heat less rapidly,[3] though it is clear from the early part of the night that, so long as thermoregulation is active, it can easily compensate for this.

Young babies, 6–12 weeks of age, have less well developed temperature rhythms.[6] In this group we see no significant effect of sleeping posture on rectal temperature at any time of night.

The night after first DPT immunisation babies show a mild, transient disturbance of their normal temperature rhythm. Rectal temperature does not fall but may even rise above the normal value for an active, awake baby, though the infant is asleep.[5] Presumably these changes are due to some mild pyrogen in the vaccine. Our final observations show that even under these conditions, where body temperature is being driven up in a way analogous to the effects of infection, the prone sleeping position is not associated with greater temperature rises.

Although we can offer some limited evidence to support the suggestion that prone babies may lose heat slightly less easily in their cots, it is clear that the normal processes of themoregulation can cope with this challenge even when babies are very well wrapped, in warm rooms, and under the influence of a mild pyrogen.

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Parental permission, information, and consent

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Abstract

One hundred and fifty parents of emergency paediatric admissions were interviewed; 60 of 106 (57%) blood samples were taken and 107 of 120 (89%) treatment regimens were instituted without their permission. Furthermore, the reasons for over half the blood tests and 31% of the drug treatments were not explained.

Consent for investigation and treatment is an important part of the doctor-patient relationship. In surgical practice written consent is obtained for operations, but in medical practice the arrangement is less clear cut. In this survey we aimed to explore this from a patient's point of view by interviewing the parents of child patients. For the purpose of the survey the concept of consent was divided into two components—permission for an investigation to be performed or drug treatment to be started and information about why the test or treatment was being undertaken.

Methods

In a paediatric hospital 150 parents of children who had been admitted through the accident and emergency department were interviewed by questionnaire (Appendix). The survey took place during a four month period and interviews were carried out by one investigator (JMEF) between one and seven days after admission while the child was still an inpatient. To be entered into the survey parents had to be English speakers and to have been with their child when he or she was admitted. Most of the parents were interviewed between 0900 and 1700, and most were mothers. The investigations (generally referred to as tests) discussed were only those that the parents had witnessed on the day of admission, whereas drugs referred to any drug given during the hospital stay.

Results

A total of 150 parents were interviewed; 142 had children who had had investigations, and 120 had children who had been given drugs.

Sixty of 106 parents (57%) whose children had had blood tests were not asked for permission before the tests. Of these, 10 thought that they should have been asked. Figures for urine tests and radiographs were 65 out of 104 parents and 47 out of 81 not asked, respectively, of whom nine who had urine tests, and eight who had radiographs, considered they should have been asked (table 1). For blood tests, urine tests, and radiographs 59 out of 106, 65 out of 104, and 30 out of 81, respectively, were not told what the test was for. Only nine of the 142 parents thought they should not have been told what the test was for.

One hundred and seven of 120 parents (89%) whose children had received drugs had not been asked for permission. Of these, 29 thought they should have been asked (table 2). Fifty two had not been told what at least one of the drugs was for, and 45 of these felt that they should have been informed (table 3). Of 240 drug treatments started parents knew what the drug was for in 166 instances.

Of 142 parents, 111 considered that permission for tests was implied by their child being an inpatient. Of 120, 104 considered that the same was true for drug treatment.

Discussion

The doctor-patient (or doctor-parent) relationship is based to a considerable extent on trust, itself the product of empathy and mutual understanding. In this survey, most parents thought either that they had given permission for tests to be done or treatment to be started and that they should be asked for permission, or that they had not given their permission but felt that such permission need not be sought. Both of these indicate that there is a trusting relationship and that the doctor is judging the parents' expectations appropriately. The degree of trust is further illustrated by the 111 of 142 parents who thought that permission for testing and the 104 of 120 who thought that permission for

Table 1 Responses to questions about permission to carry out tests

Do you think that you should have been asked for permission before tests were done on your child?	*Were you asked for permission before tests were done on your child?*								
	Yes			*No*			*Total*		
	Blood test	*Urine analysis*	*Radiograph*	*Blood test*	*Urine analysis*	*Radiograph*	*Blood test*	*Urine analysis*	*Radiograph*
Yes	31	23	22	10	9	8	41	32	30
No	15	16	12	50	56	39	65	72	51
Total	46	39	34	60	65	47	106	104	81

Table 2 Responses to questions about permission to start drug treatment

Do you think you should have been asked for permission before drug treatment was started on your child	*Was permission given for all drugs that the child received?*		
	Yes	*No*	*Total*
Yes	5	29	34
No	8	78	86
Total	13	107	120

Table 3 Responses to questions about the reason for starting drug treatment

Do you think you should have been told what drug treatments were for?	*Were parents told what the drugs given to the child were for?*		
	Yes	*No*	*Total*
Yes	64	45	109
No	4	7	11
Total	68	52	120

starting drug treatment was implied by the fact that the child was an inpatient. Even in this climate of trust, however, doctors should take account of the fact that testing without consent is an assault.[1] This is complicated when dealing with children. In adult practice, the offering of an arm for a blood test—for example—can be taken as implied consent. The child, however, may be unable to understand such concepts, and will depend instead on its parent to give consent.

This survey also shows the limited extent to which information about drugs or tests is given by some doctors. Thus—for example—over half the parents did not know the reason for the blood test that had been done on their child. This could be the result of failure to remember an explanation that had been given, but is more likely to reflect a lack of information given by the doctor. A similar lack of parental knowledge was found about drug treatment. Though a few did not wish to know what their children's drugs were for, most parents (91%) did, and yet 31% of drug treatments had not been explained. The degree to which informed consent to treatment should be obtained has been carefully considered by Dukes and Swartz.[2] Their medicolegal review of published reports states: 'There must be a sufficient explanation of the risk/benefit balance with the emphasis on risks which are either severe or frequent or both', and 'the patient must understand before he can consent'. Informed consent ranges from full disclosure for medical or surgical procedures (as is now usually practiced in the USA) to a more informal approach for minor routine treatments with everyday remedies. In general, the greater the risks, the more explicit the consent should be. The results of our survey suggest that informality in consent is being taken to an extreme in that many parents were unaware of the reason for which drugs were being given to their children, and were probably ignorant of important information such as side effects or other potential risks. This ignorance about drug treatment might adversely affect compliance.[3]

Parents clearly have a high degree of trust in doctors, but this survey suggests that the relationship between them is often less than ideal. Freidsen created the models of 'guidance/cooperation' (guidance by the doctor of the cooperating patient) and 'mutual participation' (representing the optimal relationship between the two parties),[4] yet the more authoritarian mode of 'activity/passivity' (active doctor and passive patient) that most doctors claim does not occur except in emergencies is still being widely practiced in general medical care. Increasing the amount of information given to patients (or parents) and involving them more fully in decision making about their (or their children's) sickness and health should aid movement towards the optimal relationship.

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Appendix

Patient:

Name ....

Age ....

Sex ....

Diagnosis ....

Length of stay in hospital ....

Parents:

Occupation of major breadwinner ....

Parent interviewed mother/father

Tests:

1(A) Were you asked for permission before tests were done on your child?

Blood test	Yes	No	Not applicable
Urine test	Yes	No	Not applicable
Radiograph (specify simple one—for example, chest)	Yes	No	Not applicable

(B) Do you think that you should have been asked for permission before tests were done on your child?

Blood	Yes	No
Urine	Yes	No
Radiograph	Yes	No

2 Do you think that permission for a test to be done on your child is implied by the fact that he or she is in hospital?

Yes No

3(A) Were you told what the tests done on your child were for?

Blood	Yes	No	Not applicable
Urine	Yes	No	Not applicable
Radiograph	Yes	No	Not applicable

(B) Do you think you should have been told what tests were for?

Yes No

Drugs:

Which drugs have been given to your child during this admission?

1(A) Were you asked for permission before drug treatment was given to your child?

Yes No

(B) Do you think that you should have been asked for permission before drug treatment was given to your child?

Yes No

2 Do you feel that permission for drug treatment to be given to your child is implied by the fact that he or she is in hospital?

Yes No

3(A) Were you told what the drugs given to your chlid were for?

Yes No

(B) Do you think you should have been told what drug treatments were for?

Dysequilibrium/ataxic diplegia with immunodeficiency

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Abstract

A girl with purine nucleoside phosphorylase (PNP) deficiency is described. The nature of the motor disorder is similar to other children since found to have PNP deficiency. It is suggested that the diagnosis be considered in any child with unexplained dysequilibrium/ ataxic diplegia. Other previously unreported features are intracytoplasmic neutrophil inclusion bodies and an improvement in the neutropenia after intravenous immunoglobulin.

Severe congenital immunodeficiency states generally present with recurrent infections as maternal passive immunity declines. Children with purine nucleoside phosphorylase (PNP) deficiency can, however, present with a non-progressive motor disorder before the onset of the immunodeficiency giving an opportunity for treatment before secondary complications occur and for genetic advice. This requires a clearer definition of the nature of the motor disorder than had previously been available.

Case history

A 1 year old girl presented with delay in motor development. She had been rolling since 9 months, could sit supported only with a 'C' shaped back, and could not crawl or weight bear. She gave the appearance of hypotonia, although examination demonstrated slightly increased tone and brisk reflexes. She could use her hands crudely, tucking in her thumbs, but had a full range of supination. She appeared bright and alert. Birth had been normal with a birth weight of 4400 g. Her parents were healthy and unrelated. Computed tomography of the brain was normal. She learned to sit, propping herself, at 16 months and at 19 months was able to pull herself to standing. Although her balance remained very poor, she was able to walk with her hands held at 26 months and at 3 years take a few unsteady steps. Fine hand movements were mildly ataxic, her speech clear, and intellectual development normal.

At age 26 months she began to suffer severe recurrent urinary tract infections despite prophylactic antibiotic treatment. She had had no previous significant infections. Ultrasonography showed pelvicaliceal dilatation, progressing to frank hydronephrosis within six months. A micturating cystogram confirmed severe vesicoureteic reflux. Haematological indices were normal at 33 months.

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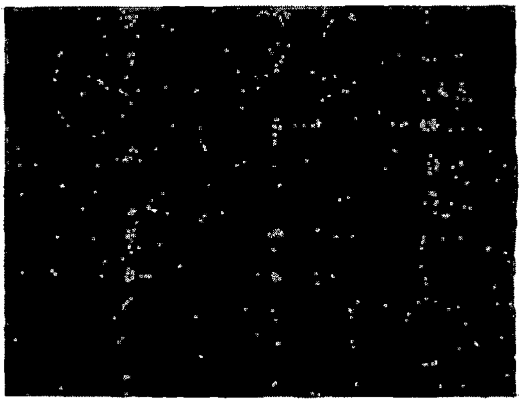

Intracytoplasmic inclusion in peripheral blood neutrophil (haematoxylin and eosin stain×1000).

When admitted with a further urinary tract infection at 3 years she was noted to have oral candida, right cervical lymphadenopathy, and to be both neutropenic (neutrophil count $1{\cdot}0\times 10^9$/l) and lymphopenic (lymphocyte count $1{\cdot}2\times10^9$/l). A bone marrow aspirate showed megaloblastoid nuclei, dyserythropoiesis, and myeloid maturation arrest with bizarre intracytoplasmic inclusion bodies; this was also seen in peripheral blood neutrophils (figure). Immunoglobulins were normal, tetanus toxoid antibodies were present in normal amounts, isohaemagglutinins were weakly present, nitroblue tetrazolium test was equivocal, and HIV antibody was negative. Total lymphocyte and T_4 and T_8 subset numbers were severely depressed ($0{\cdot}4\times10^9$/l, 0×10^9/l, and $0{\cdot}02\times10^9$/l respectively) and were functionally unresponsive to mitogens. Adenosine deaminase activities were raised, however, and PNP was absent. Maternal and paternal values were 53% and 55% of normal respectively. A lymph node biopsy specimen showed lymphoblastic/immunoblastic non-Hodgkin's lymphoma.

Her clinical condition deteriorated and as there was no compatible bone marrow donor it was decided, after discussion, to give purely palliative lymphoma treatment. The child died 20 days later.

Discussion

PNP deficiency was first described in 1975.[1] Enzyme substrates inosine, deoxyinosine, guanosine, and deoxyguanosine accumulate and enzyme products urate and guanosine triphosphate are depleted. The principle systems affected are the lymphoid system and central nervous system.

Neurological dysfunction primarily affecting motor development is clearly recognised in association with PNP deficiency, often being the presenting feature.[2] The characteristics of the motor disorder have not been clearly defined, however, with previous papers referring to spastic quadriplegia or spastic diplegia.[2 3]

Two siblings described as having familial dysequilibrium/diplegia with T lymphocyte deficiency[4] have now retrospectively been found to have PNP deficiency, using cultured fibroblasts, at this hospital. Both parents had heterozygote values for PNP. These children were thought to be similar to those described by Hagberg *et al* as having familial ataxic diplegia with deficient cellular immunity.[5] The four children described in these two papers, plus our own case, point to a fairly characteristic and identifiable clinical picture. This would seem to consist of a disequilibrium—that is, pronounced difficulty in maintaining posture and upright position giving rise to an early hypotonia, very unsteady and delayed sitting, and great difficulty in walking independently. In contrast there is either no, or only a mild, intention tremor or clumsiness. There is evidence of a spastic diplegia on clinical examination with brisk reflexes, upgoing plantars, and sometimes ankle clonus and restriction of passive dorsiflexion of the ankles. When walking this is masked by trunkal ataxia, however, particularly as the child gets older. The neurological picture appears to be non-progressive, may relate to the degree of guanosine triphosphate depletion and is non-infective in aetiology.[2] Intelligence may be normal as in this case.

The haematological and immunological consequences of PNP deficiency relate to the depressed T cell numbers and function, leading to repeated infections with viral illnesses often being the cause of death. These children should not receive live vaccinations. Lymphomas, often of a B cell origin, are also a complication of other immunodeficiency states, for example, AIDS, and have been described in PNP deficiency.[3]

Haematological findings in PNP deficiency are pure red cell aplasia, megaloblastic anaemia, autoimmune haemolytic anaemia,[2 6] and maturation arrest at the myelocyte/metamyelocyte stage in bone marrow aspirates.[3] Intracytoplasmic neutrophil inclusions (figure) have not been previously described; they persisted after resolution of sepsis and in addition, identical inclusions were seen in the paternal blood film. Similar inclusions are well recognised during treatment with drugs that interfere with DNA synthesis such as azathioprine, chlorambucil, and appear to be fragments of DNA. DNA synthesis is impaired in PNP deficiency suggesting a similar aetiology.

Autoimmune disease is another complication of immune deficiency including PNP deficiency.[2] Suspecting the neutropenia to be immune mediated, we treated our patient with 2 g/kg intravenous immunoglobulin over two days. There followed a dramatic rise in the neutrophil count ($0{\cdot}4\text{–}2{\cdot}8\times10^9/l$). The patient had been persistently neutropenic for two months before this.

In conclusion, recognition of PNP deficiency before onset of severe infection or malignancy is important so that bone marrow transplantation from a suitable donor can be considered while the patient is well. Successful engraftment has already been documented in this condition.[3 6] In addition, antenatal diagnosis is now possible for measuring PNP in chorionic villus samples. We consider familial dysequilibrium/diplegia with T lymphocyte deficiency and familial ataxic diplegia with deficient cellular immunity should no longer be considered separate disease entities, but reclassified as cases of PNP deficiency.

We thank Mr R Webber for his photographic and technical assistance.

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Fulminant hepatitis B in an infant born to a hepatitis Be antibody positive, DNA negative carrier

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Abstract

A boy was born to a mother who was a chronic hepatitis B virus (HBV) carrier. She was hepatitis Be (HBe) antibody positive and HBe antigen and HBV-DNA negative. The boy had not received hepatitis B vaccine and died from fulminant hepatitis at 3 months of age. This case demonstrates the need to vaccinate babies of HBe antibody positive, HBe antigen negative carriers.

Perinatal transmission of hepatitis B virus (HBV) is well documented in babies born to hepatitis Be (HBe) antigen positive mothers.[1] Risk of contamination as well as natural history when the mother is HBe antigen negative is underestimated, however, and these babies are not always given HBV vaccination. We report the case of a child who died from fulminant hepatitis B and who was born to a HBe antigen and DNA negative mother.

Case report

A boy was born at full term to a healthy HBV carrier. She was hepatitis B surface (HBs) antigen positive, HBe antigen negative, hepatitis B core (HBc) IgG antibody positive, HBe antibody positive, and HBV-DNA negative. The boy was not vaccinated and did not receive immune prophylaxis at birth. He had no contact with any other known HBV carrier.

At 3 months old he was admitted to hospital because of vomiting, failure to thrive, jaundice, and hepatomegaly. He was irritable. Liver and spleen were not palpable and he had mild ascites. Biochemical investigations are shown in the table. He was HBc IgM antibody positive, HBs antigen positive, HBe antigen negative, and HBe antibody positive. Serology for hepatitis A virus, cytomegalovirus, Epstein-Barr virus, HIV, and toxoplasmosis were negative. He had passive immunisation for rubella and herpes simplex virus. His urine was sterile. He had received no sucrose and no drugs, and urinary reducing substances were negative. Erythrocyte uridyldiphosphate galactosyl transferase activity and serum tyrosine concentrations were normal. Liver ultrasonography showed appreciable parenchymal atrophy, normal biliary tract, and ascites. He was registered on the urgent list for liver transplantation and was admitted to the intensive care unit. Within 24 hours his condition deteriorated, encephalopathy progressed, and he died from liver insufficiency.

His mother's HBV serological markers were identical to those at her prenatal investigations and there was no HBV-DNA detected in serum by liquid phase molecular hybridisation (Abbott).

Discussion

It is commonly thought that the risk of HBV transmission is absent or low when the hepatitis B carrier mother has developed anti-HBe antibodies.[2] Because of this, babies born from these mothers may not be vaccinated at birth against hepatitis B in developed countries. The risk of perinatal transmission is related to HBs antigen titre, HBe antigen positivity, and HBV specific DNA or DNA polymerase activity in maternal serum.[1 2] However, case reports have shown that anti-HBe antibodies do not protect fully against HBV transmission, and 10 to 20% of babies born to HBs antigen positive, HBe antibody positive mothers may be infected.[3 4] In one series half of these developed acute or even fatal hepatitis B.[4] It is not known if maternal serum contained HBV-DNA in these cases. The present report demonstrates that even when no HBV-DNA is detected by hybridisation in serum of HBs antigen positive mothers, babies are at risk of developing postnatal hepatitis B. Mild viral replication can be present despite negativity of serum HBe antigen and HBV-DNA,[5] and it is likely that the baby was contaminated at birth by maternal serum containing traces of HBV-DNA that was not detectable by DNA hybridisation. The child had had no contact with any other HBV carrier.

Results of biochemical investigations (normal results are shown in parentheses)

Total bilirubin	246·2 µmol/l (<17·1)
Direct bilirubin	85·5 µmol/l (<3·4)
Aspartate aminotransferase	128 IU/l (<25)
Alanine aminotransferase	1223 IU/l (<32)
γ-glutamyltransferase	38 IU/l (<45)
Total serum protein	43 g/l
Albumin	32 g/l
Prothrombin time	>20 seconds
Glucose	6·9 mmol/l
Ammonia	91·6 µmol/l (<58·7)
Haemoglobin	88 g/l
White cell count	3·12×10⁹/l (neutrophils 27%, lymphocytes 51%)
Platelet count	421×10⁹/l

It is not known why when the mother is HBe antigen negative and HBs antigen positive the risk is greater of developing a severe or even fulminant hepatitis than in babies born from HBe antigen positive mothers.[3 4] The host immunological response to infection is responsible for the hepatocellular lysis instead of the virus itself. Infants from HBe antigen negative mothers may be exposed to low doses of HBV particles and may develop an overwhelming response to infection causing massive immune medicated damage. On the other hand infants from HBe antigen positive mothers receive a lot of HBV. The capacity of their immune system to fight the infection might be exceeded and they do tend to become chronic asymptomatic carriers.[3 4] It has also been suggested that HBV mutation may modify the course of chronic hepatitis and might prevent formation of normal HBe antigen.[6] If this was the case in our patient we would have expected to find HBV-DNA in maternal serum.

No other cause of liver disease was found in our patient. Although liver transplantation has not been performed in this particular situation in infants, the procedure can be successful in small children and the boy was therefore registered on the waiting list.[7] He unfortunately died before any donor could be found.

Our case report shows that HBe antibodies do not protect against perinatal HBV mother to child transmission, and that babies from HBe antibody positive, HBV-DNA negative carrier mothers are at risk of developing fulminant heptitis B. They should therefore also be included in vaccination programmes against hepitis B.

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Long term survival after heart transplantation for doxorubicin induced cardiomyopathy

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Abstract

A 10 year old child developed severe cardiomyopathy after combined, multicycle chemotherapy for Ewing's sarcoma and was treated by heart transplantation with good results. Long term azathioprine and cyclosporin caused only mild impairment of immune function and there were no recurrent infections, local recurrences of the tumour, or distant metastases.

Ewing's sarcoma is a malignant, round cell tumour of bone that occurs in later childhood and adolescence, which has a poor prognosis.[1,2] Before the era of combination chemotherapy the five year survival rate was 5 to 10%.[1] Aggressive chemotherapy has resulted in a mean three year disease free survival of almost 60%.[3] This improvement is mainly the result of systemic chemotherapy, with better staging of patients or more efficient radiation regimens playing a small part.

Doxorubicin hydrochloride (Adriamycin) is an essential drug in combined, multicycle chemotherapy,[1,2] although it is known (together with related drugs) to cause a cardiomyopathy that is usually dose dependent.[4]

We describe a child who, having developed a severe cardiomyopathy after combined, multicycle chemotherapy for Ewing's sarcoma, underwent heart transplantation with good results.

Case report

An 8 year old boy with Ewing's sarcoma of the pelvis and proximal femur was treated with a four drug combination of chemotherapy (vincristine, cyclophosphamide, dactinomycin, and doxorubicin hydrochloride), plus local irradiation (protocol POG 8095), and conservative surgery. The total dose of doxorubicin that he received was 480 mg/m^2. Despite regular monitoring of cardiac function by electrocardiography and echocardiograph scanning, severe cardiomyopathy developed 25 months after the diagnosis had been made. Cardiac function rapidly worsened and was soon so impaired that several episodes of congestive failure occurred during the subsequent weeks, leaving the child bedridden.

Twenty nine months after the diagnosis of Ewing's sarcoma and four months after the onset of cardiomyopathy, the child, by then 10 years old and with no evidence of residual tumour, underwent orthotopic transplantation of a heart from an 8 year old child who had been killed in a car accident. The postoperative course was uneventful. Signs of rejection were monitored by serial myocardial biopsies, and prevented by oral immunosuppressive drugs cyclosporin (5 mg/kg/day), methylprednisolone (2 mg/kg/day), and azathioprine (62·5 mg/day). During the next few months the steroids were reduced to 5 mg daily.

More than three years after transplantation the child is doing well: his heart function is normal, he attends school, and he is able to take part in normal physical activities. Repeated checks indicate that there is no local recurrence or distant metastases. His serum immunoglobulin concentrations were: IgG 14·5 g/l, IgA 4·7 g/l, and IgM 1·8 g/l. IgG subclass values were: IgG_1 8·1 g/l, IgG_2 1·8 g/l, IgG_3 1·3 g/l and IgG_4 0·3 g/l. Peripheral blood T lymphocyte subsets were: CD3+ 83%, CD4+ 47%, CD8+ 55%, CD11+ 83%, CD20+ 26%, and CD16+ 6%. Lymphocyte proliferative response to phytohaemagglutinin in vitro was 71·7% of normal controls. Delayed type hypersensitivity skin testing evoked no response to any of the challenged antigens.

Discussion

Ewing's sarcoma is a malignant bone tumour that had a poor prognosis until combined chemotherapy including anthracyclines was introduced. The current five year disease free survival rate is about 60%. Bacci *et al* recently reported a 7% risk of late relapse after that time, confirming other reports.[3]

We have reported a child who, 25 months after the diagnosis of Ewing's sarcoma, had achieved persistent local and systemic control but suffered from life threatening cardiomyopathy. The decision to attempt heart transplantation was difficult to take. On the one hand it was indicated because of the poor quality of the child's life and the lack of any other possible cure for his severe cardiomyopathy; on the other hand his underlying malignant disease was a major obstacle. Now, more than three years later, that choice seems to have been correct. The child has regained a completely normal life: he attends school, has normal heart function, and is able to take part in normal physical activities.

Because of the improvement in cure rate provided by combined treatment of some childhood cancers, the limits for indication of organ transplantation may well be revised. We are aware that a few children with cancer have recently undergone heart transplantation (J Le Bidois, Paris, personal communication[4]), and this treatment is also being given for some non-malignant chronic diseases of children.[5]

The mechanisms of development of distant tumour metastases are not yet completely clarified. A possible role for immune surveillance has been postulated but is still under investigation. In the present case long term immunosuppressive drugs, given to prevent graft rejection, could cause some depression of the immune system, and possibly enhance the risk of tumour recurrence. To assess the real degree of immune depression we had induced in this patient, we tested his immune function. Humoral immunity, assessed by serum immunoglobulin concentrations, was normal. Cellular immunity was also substantially normal. Only the delayed type hypersensitivity skin test reactions, reliable markers of overall immune function, were persistently depressed, as is also seen in children undergoing chemotherapy for leukaemia.

To conclude, heart transplantation succesfully cured doxorubicin induced cardiomyopathy despite the underlying tumour. Long term administration of steroids, azathioprine, and cyclosporin caused only mild impairment of immune function; he had no recurrent infection, local recurrence of tumour, or distant metastases.

With continuing advances in our understanding of tumour biology and the techniques of organ transplantation, eligibility criteria for transplantation should continually be re-evaluated. Nevertheless further experience is necessary before this becomes the accepted treatment.

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Life threatening 'epilepsy'

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Abstract

A 5 year old girl presenting with episodes of sudden loss of consciousness was found to have intermittent ventricular tachycardia and, on one occasion, self limiting fibrillation. Corrected QT interval was normal. After several therapeutic measures clinical and electrocardiographic improvement was achieved by administration of sotalol.

We present the case of a girl with a sudden loss of consciousness that was thought to be caused by epilepsy.

Case history

The patient, a 5 year old girl, was admitted to hospital having collapsed at home. She was found by her mother unconscious, limp, and cyanosed. She had been incontinent of urine and faeces. She recovered after four minutes and appeared confused. She had been born after 42 weeks' gestation by caesarean section for fetal distress evidenced by meconium staining. She had been referred to a paediatric neurologist at 3 years of age with a history of never running. The only abnormalities at that time were mild generalised hypotonia and a slightly broad based gait suggestive of a mild degree of ataxia. Her physical state was thought to be in keeping with a benign congenital hypotonia. At nursery she was noted to have poor fine hand movements and was referred for occupational therapy. Fifteen days before this admission she had tripped and banged her head on the floor. She was then unconscious for four minutes. Skull radiography had shown no fracture and observations overnight in hospital had been normal. A cousin had been investigated for recurrent hypoglycaemia when aged 2 years and ketotic hypoglycaemia diagnosed.

On admission she was fully conscious and alert. Her height was on the 97th centile and weight on the 75th. Cardiovascular, respiratory, and abdominal examinations were normal. She was a clumsy girl with mildly ataxic gait but no other neurological abnormality. Blood biochemistry including fasting blood glucose was normal. Computed tomography of her brain, a 12 lead electrocardiogram (ECG), and an electroencephalogram also gave normal results.

A month later she was again found unconscious. As before there were no witnesses of her behaviour or activity level before her collapse. On admission the only abnormal finding was an irregular pulse. Electrocardiography showed sinus rhythm with intermittent junctional beats. A 24 hour ECG showed episodes of sustained polymorphic ventricular ectopics and ventricular tachycardia. Exercise testing, with intensive care cover, did not produce any arrhythmia; in particular the QT interval did not alter. Cardiac ultrasound scan was normal. Disopyramide treatment was commenced and therapeutic concentrations attained. A CardioMemo system was supplied to the family and its use demonstrated. This small instrument is held against the bare chest during any abnormal episodes and a button pressed to record a 32 second electrocardiographic strip. This recording can then be transmitted by telephone to a monitoring service at the hospital. Several days later this method demonstrated for the first time that collapse of the patient, during normal quiet activity, coincided with an episode of ventricular tachycardia. Flecainide was commenced after readmission to hospital and commencement of continuous electrocardiographic monitoring. Later the same week an episode of self limiting ventricular fibrillation was accompanied clinically by a complaint of sore knees but no loss of consciousness. The blood flecainide concentration was found to be within the therapeutic range. Electrophysiological studies failed to initiate any arrhythmia. Sotalol treatment was commenced. The ECG showed an appreciable improvement with only occasional ventricular ectopics. There have been no further episodes of collapse.

Discussion

Before concluding that acute loss of consciousness is due to epilepsy a number of investigations are generally considered mandatory to rule out anatomical, electrolyte, infective, metabolic, or neoplastic disturbances. In this case the history was misleading in two respects. Firstly, the possibility of asphyxial damage at birth was raised by the presence of meconium and subsequent poor gross and fine motor coordination; this was excluded by review of the neonatal record and normal brain tomography. Secondly, there was a second degree relative who had suffered intermittent hypoglycaemia, but a prolonged fast in this patient failed to produce hypoglycaemia.

Twelve lead electrocardiography, routine as an investigation for interruption of normal consciousness in this unit, was unrewarding. Garson reports the separate sudden deaths of two siblings whose mother was subsequently found to have a prolonged QT interval.[1] Garson therefore recommends the calculation of the corrected value QTc (divided by the square root of the length of each cardiac cycle in seconds), although this has been disputed.[2 3] In this case QTc before commencement of treatment was not prolonged (0·37 seconds) at rest or during exercise. Previous reports of patients with normal QT and QTc values and yet suffering recurrent syncope due to ventricular fibrillation suggest a forme fruste of the long QT syndrome.[4]

The nature of the episodes (sudden falls or 'drop attacks') together with the finding on one occasion of an irregular pulse nevertheless strongly suggested the possible involvement of an arrhythmia. Although a 24 hour ECG did reveal intermittent ventricular tachycardia, it was not until some time later with the aid of a CardioMemo system that one of the patient's attacks was found to coincide with the arrhythmia. The lesson learnt is that during the investigation of such symptoms in the presence of a normal electroencephalogram, efforts to exclude a causal cardiac arrhythmia should proceed via 12 lead ECG, 24 hour monitoring, and CardioMemo systems without delay in order to prevent further life threatening episodes.

Once the diagnosis was reached it proved difficult to find a suitable treatment to decrease the frequency and severity of ventricular arrhythmia. As a class Ic antiarrhythmic agent flecainide acts as a membrane stabiliser to reduce myocardial excitability with no effect on action potential duration. Unfortunately proarrhythmia may occur in patients with ventricular arrhythmia. This treatment was therefore initiated under continuous electrocardiographic monitoring and terminated after one episose of self limiting ventricular fibrillation. Sotalol was used next as it is a drug with a wide range of action by reason of its combined β blocking activity (class II antiarrhythmic action) and its property of prolonging the action potential duration in myocardial tissues (class III action). The case described here supports available data which indicate that sotalol is an effective antiarrhythmic compound for a significant number of patients with life threatening ventricular tachycardia/ventricular fibrillation refractory to conventional antiarrhythmic drugs.[5]

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Ultrafiltration for intractable ascites after liver transplantation

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Abstract

A 5·7 year old boy with α_1-antitrypsin deficiency developed intractable ascites after liver transplantation. Conservative treatment was unsuccessful and after 18 days concentrated ascitic fluid was reinfused intravenously using a Gambro haemofilter. The ascitic loss resolved rapidly. This new method of ultrafiltration proved simple and effective.

Case report

Severe intractable ascites was the main indication for liver transplantation in a 5·7 year old boy with α_1-antitrypsin deficiency. After the operation the ascites returned and massive amounts were lost through the abdominal drains from the fourth postoperative day. The next day the serum bilirubin concentration and alanine transaminase activity rose and ultrasound Doppler demonstrated poor hepatic compliance. These are all indications of possible acute rejection.

A liver biopsy specimen confirmed moderately severe rejection and treatment with high dose intravenous methylprednisolone was given for three days. There was a rapid response with the liver function tests returning to normal within seven days. The ascitic fluid losses, however, increased to a maximum of 10 l/day. The fluid lost was a sterile exudate which contained 39 g/l of protein. Repeated examinations with ultrasound Doppler excluded obstruction of the inferior vena cava and the hepatic and portal venous systems. Despite massive replacement with blood products the protein loss caused a severe coagulopathy (fig 1). From the 11th day all ascitic fluid loss was reinfused intravenously. This rapidly corrected the coagulopathy but the volume of ascites remained the same (fig 1).

After 18 days it was decided to concentrate the ascitic fluid using a Gambro Haemofilter FH22 (Gambro Dialysatoren) before reinfusion. In a closed circuit the ascitic fluid was drained through a peritoneal catheter, then pumped across the haemofilter membrane. The protein concentrate was then reinfused through a blood transfusion filter (Pall) into a femoral vein (fig 2). The volumetric infusion pump (IMED) was set at a rate between 100 and 600 ml/hour, starting with a high rate initially while the abdomen was grossly distended and decreasing as the abdominal girth diminished. The filtrate, which varied in volume from 100 to 150 ml/hour, was discarded. The haemofilter was perfused with heparin at a dose of 100 units/hour to prevent blockage of the filter and clot formation in the ascitic fluid. No prophylactic antibiotic treatment was used and ascitic fluid sent daily for culture remained sterile. Transient hyponatraemia and oliguria occurred on the third day of the procedure but the serum urea and creatinine concentrations remained stable. After six days the abdominal girth had decreased from 80 cm to 65 cm and ultrafiltration was stopped. Subsequently there was only slight ascitic drainage, and this ceased entirely after two days.

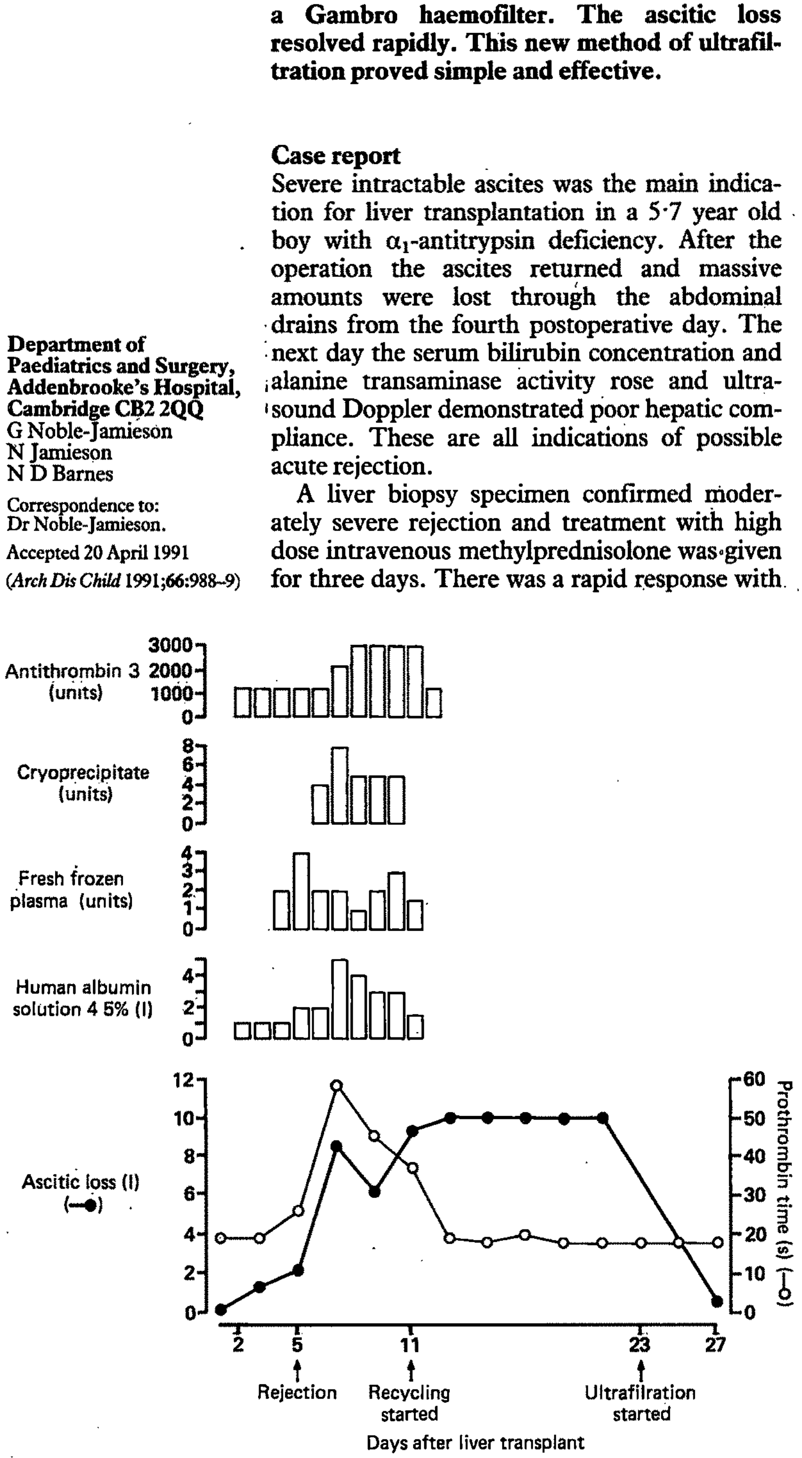

Figure 1 Blood product requirements and changes in prothrombin time in relation to ascitic fluid losses.

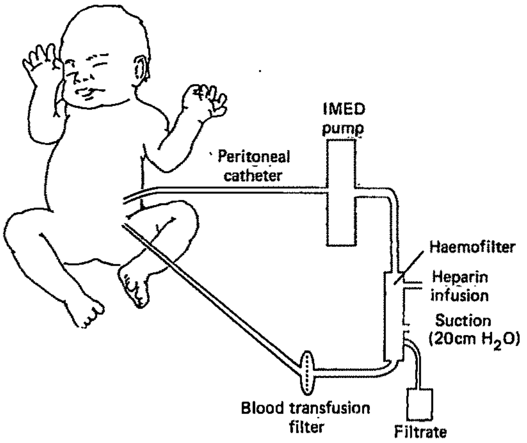

Figure 2 Circuit for ultrafiltration and reinfusion of ascites.

Discussion

In liver cirrhosis ascites formation is a consequence of progressive intrahepatic venous obstruction, leading to a rise in intrasinusoidal pressure and increased hepatic lymph production.[1] Another important mechanism is the hyperaldosteronism and urinary sodium retention which occurs in response to the depletion of the vascular space.[1 2] Even when there has been gross ascites preoperatively it generally resolves promptly after successful liver transplantation. Among 120 recipients of paediatric liver transplant, only three children have developed severe postoperative ascites, on each occasion in association with acute graft rejection. Ultrasound Doppler studies have proved extremely useful in the early diagnosis of acute rejection by demonstrating a reduction in hepatic venous pulsatility, indicating a swollen and noncompliant liver.[3] These changes reflect reduced hepatic venous outflow and ascites formation may follow. Depletion of the intravascular space leads to renin, angiotensin, and aldosterone secretion and so to urinary sodium retention. This secondary hyperaldosteronism probably contributes to prolonged ascitic loss even after a rejection episode had resolved. It seems probable also that the severe preoperative ascites may have opened channels for ascitic fluid production.

Thus the rapid development of ascites after liver transplantation may indicate the onset of acute graft rejection. When venous obstruction has been excluded a liver biopsy is needed. Management should include control of the rejection and treatment of the ascites. Replacement of large volumes of plasma proteins may be required to replenish the intravascular volume, to maintain normal coagulation, and to maintain humoral immunity. Diuretics, especially aldosterone antagonists such as spironolactone, are usually given to counteract the secondary hyperaldosteronism. When these forms of treatment prove inadequate it seems logical to replace the ascitic fluid loss, and various methods of reinfusion and ultrafiltration have been described.[4–6] The ultrafiltration device most commonly described has been the Rodiascit system, which allows continuous ultrafiltration and reinfusion of the concentrated ascites. We used a less complicated and more readily available method for ultrafiltration of ascites. Continuous arteriovenous haemofiltration is a well established technique and is frequently used for patients with oliguria and fluid overload. The haemofilter removes water and crystalloids with a molecular weight below 15 000. Filtration is usually driven by arterial pressure alone but can be enhanced by a pump and this was of course needed to circulate the ascitic fluid. By recycling the ascites in this way protein losses were avoided and the clotting deficit was rapidly corrected. Immunoglobulins and complement are also lost in ascitic fluid and their retention reduces the risk of infection. To our knowledge this method of ultrafiltration of ascites has not been used before and it proved remarkably simple, practical, and effective.

We thank the nursing staff of the paediatric intensive care unit for their technical advice and expertise in caring for this patient.

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CURRENT TOPICS

The Oregon formula: health economists' dream or Stalinist nightmare?

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The television programme *Dispatches: The Oregon Formula* (Channel 4, November 24, 1990) described a remarkable attempt to establish health care priorities in the state of Oregon. In a masterly presentation, it was explained how the Oregon formula relates the cost of a medical intervention to its benefits, measured in quality adjusted life years (QALYs) gained. Treatments are then ranked according to the cost of producing one QALY. At the top of the list is the cheapest, next is the second cheapest and so on. The intention is that the Oregon Health Services Commission will allocate its budget by first purchasing the cheapest QALYs, then the second cheapest and will move down the list until the budget is exhausted. Procedures ranked below the cut off point will not be offered.

The Oregon Health Services Commission is not exactly comparable with the British National Health Service (NHS) since most middle class Oregonians are covered, to a greater or lesser extent, by health insurance schemes. The Oregon experiment will apply only to treatment for those low income families which qualify for public assistance. Private insurance is much less common in the UK, but the significance of the experiment for the NHS is only too apparent. Scarce resources are allocated in the NHS by a mixture of formal and informal devices. The Resource Allocation Working Party (RAWP) formula, queues, and clinical discretion all play a part in determining whether a patient is treated. Decisions to treat, or not to treat, are frequently implicit rather than explicit, and are not always defensible either on grounds of equity or efficiency.

Under the new arrangements for the NHS, purchasers of health care will make contracts with providers of care, and in that process priorities will become explicit. Hard choices have to be made, and the Oregon approach is the only comprehensive system for making these decisions. This paper indicates areas of concern in applying the Oregon formula, or some variant of it, to the NHS and speculates on how the paediatric specialties might fare in a system of this sort.

The QALY concept

The QALY concept has become familiar to clinicians through the work of Alan Williams and his colleagues at York University.[1] It is a brave attempt to strike directly at the hardest problem in health economics, which is to measure medical output.

Some few medical interventions can be justifiable solely in economic terms. Malaria eradication programmes can 'pay for themselves' in enhanced agricultural productivity; and improved therapies for low back pain could be similarly profitable in averting working days lost due to ill health. Rehabilitation for employment is a valid part of some health care evaluations, but economists have never been comfortable with valuations of health care benefits based solely on the potential earnings of healthy people. This method is difficult to apply in the presence of widespread unemployment, cannot be used to justify the treatment of the elderly or the severely disabled, and gives the impression that economists believe man to have been created for the Confederation of British Industries.

Many health care evaluations avoid measuring the benefits of health care by using cost effectiveness analysis, which seeks to find the method of least cost for achieving a well defined objective. Cost effectiveness analysis is widely used but is not appropriate in all circumstances. Alternative therapies may differ significantly in the process by which outcomes are achieved, and it is often difficult to be certain that the outcomes are identical.

Cost utility analysis has much in common with cost effectiveness but focuses directly on the welfare of the patient by seeking alternative means of producing QALYs. The quality of life is estimated on a 0–1 scale on which 0·00 is dead and 1·00 is well. A large and increasingly sophisticated literature explores alternative methods of measuring the quality of life, but in most areas the work is scarcely beyond the experimental stage.[2] There is no consensus on how valuations of health should be made and whose opinions should be taken into account. Many studies measure health on disability and distress scales and value these according to the opinions of knowledgeable, or interested, parties such as clinicians, nurses, patients, and parents.[3 4] An alternative approach, used by the Oregon Health Commission, is to sample public opinion by telephone interviews. This method is fast, cheap, and democratic but requires members of the public to express opinions in areas where they may have no experience.

A final point concerns the way in which QALYs are calculated, and this may be of particular importance in paediatrics. In health care evaluation both costs and benefits are discounted at a conventional rate to enable comparisons to be made between alternative treatments which may differ in the timing of their costs and benefits.[5] Medical interventions involve initial costs, and sometimes a stream of other expenditure over many years. It is not legitimate to add up costs incurred at different points of time. A pound today is not the same as a pound tomorrow. This has nothing to do with the rate of inflation. If the discount rate is 5%, the present discounted value (PDV) of £100 in a year's time is the amount which, invested at 5%, will yield £100 in a year's time. It is £95·24.

Discounting a stream of costs by applying compound interest in reverse, reduces the whole cost of a treatment to its PDV which can then be compared with the PDV of alternative treatments. In the same way, and for the same reason, benefits are also discounted. Where the benefits of care are expressed in utility terms, discounting reduces the weight attached to life, and the quality of life in the more distant future.

If time horizons are short, as in the care of the elderly mentally ill, the choice of a discount rate may not be critical to the outcome of an economic evaluation. However, PDVs are highly sensitive to discount rates over long time periods such as those which are relevant in paediatric medicine. One year of full quality life in 40 years' time, discounted at 5%, has a PDV of 0·1420. At 10%, the PDV of one year of life in 40 years' time falls to 0·0221. In general, the longer the time period under consideration and the higher the discount rate, the less is the value that will be attached to future benefits.

Merits of QALYs

Cost utility analysis is a powerful and flexible technique which, in principle, can be applied to any medical treatment. Early applications have tended to concentrate on new expensive, life saving technologies. This bias in economic evaluation is explained partly by the sensitivity of the NHS to capital expenditure, and partly by the pressure on clinicians in new fields, such as renal medicine and neonatology, to justify their budgets. Cost utility analysis has the potentiality to correct this bias since it is equally applicable to low technology medicine, and to therapies which may improve the quality of life without necessarily extending life expectancy.

Far more work is needed in the more mundane medical areas but it has already been suggested by Bryan *et al* (S Bryan, D Parkin, C Donaldson. Paper given to Health Economists Study Group, London, 1988) that, for some patients, chiropody may rank high on an Oregon 'type' list. It is also likely that as more treatments are evaluated, many therapies with low unit costs will prove to be extremely expensive in terms of the cost per QALY gained.

In praise of the Oregon experiment, it can be said that no other health system has tackled the problem of scarce resources so directly by flatly and openly denying treatment to some categories of patients. Priorities are explicit and open to debate and revision. The system is also allocatively efficient in that it produces, in the opinion of those consulted, the maximum output of QALYs for a given budget.

In some ways, the Oregon priority system seems harsh but if a similar approach was adopted in the UK, it need not follow that low priority patients would not be treated. The Oregon system limits the liability of a NHS but does not preclude the financing of some treatments by other means. Private insurance and voluntary agencies could cope in some areas, and government might set up special funds in others. There is, for instance, a strong case for the separate funding of experimental medicine which would not rank high on an Oregon type list.

Is paediatrics special?

In most respects, cost utility analysis in paediatric specialties does not seem much different from adult medicine, but certain problems common to all health care evaluation apply with special force in the treatment of the unborn and the newly born. The ranking of treatments according to the cost per QALY gained depends on the cost and the effectiveness of the therapy, the discount rate which is applied, and the opinions of those consulted.

The importance of cost is self evident but it is worth noting that at least one treatment, the provision of intensive care, is generally believed to be cheaper per unit of care for infants than adults. It is also possible that some paediatric treatments would rank high on the Oregon list because some children respond better to surgery and to drug therapy than do some adults. To take one rather specialised example, drug addicted infants are weaned off heroin in a matter of days, presumably because there is no psychological dimension to their addiction.[6] By contrast, relapse rates from adult detoxification programmes are about 75%.

In one other respect paediatric interventions should fare well in a cost per QALY ranking. By comparison with health care for adults, a successful paediatric intervention generates a large quantity of life. On the other hand, improved treatments have increased the prevalence of many disabling illnesses such as cystic fibrosis, diabetes mellitus, and childhood leukaemia.[7] A less than fully successful intervention that results in the survival of an impaired child imposes costs over a whole lifetime.

The importance of discounting has been discussed in the previous section. Where paediatric interventions have long term implications, the selection of a discount rate is likely to be critical and, as there is no 'correct' rate, evaluations should always test the sensitivity of findings to variations in discount rates. It might be argued that the discounting process discriminates against treatments with long pay off periods, but this tendency is corrected, at least partially, by the discounting of long term costs.

The discount rate should reflect the riskiness of outcomes. This is important in evaluating paediatric medicine in low income countries with high child mortality rates, where the expected benefits of treatment are reduced by the probability that an infant may succumb to some other disease. This possibility is not usually considered in western countries where infectious diseases are no longer a major cause of mortality, but there are other problems in estimating the short and long term medical outcomes for infants.

In neonatal intensive care and in many other areas random trials cannot be conducted, so it is difficult to predict how infants might fare if they were not treated. Difficulties also exist in predicting the length and quality of life which an infant survivor might expect. Most severe impairments become evident at an early stage, but preliminary indications from a study of infants of low birth weight in the Mersey region, who are now aged 8–9 years, show that some disabilities, particularly deafness, were not detected at the age of 4 years. The study is also identifying quite major differences in physical and educational development between these infants of low birth weight and a control group (POD Pharoah, CJ Stevenson. Paper given at British Paediatric Association Annual Meeting, Warwick, 1990). Still subtler differences which might affect social integration and employment prospects may not become evident for some years to come. Long term follow up studies do not exist for many therapies, both old and new, so estimates of QALYs gained from a wide range of treatments must be subject to uncertainty.

Decisions to treat the unborn and the newly born infant are inextricably linked with consideration of the sanctity of life. This is not peculiar to paediatrics and bears equally on the care of the elderly and the terminally ill. However, perinatal care is special since the infant's preferences cannot be consulted and the neonatologist is, of necessity, bound to treat the family as well as the patient. A bald estimate of the QALYs which an infant might expect from treatment may therefore underestimate the value of medical output to the whole family.

One aspect of paediatrics is unique in medicine. Provided that parents are capable of producing other children, a paediatric intervention which saves a life is not a pure gain, since it might displace another child. Replacement demand is not much discussed in the economics of neonatal intensive care, but it has been considered in the literature on the economics of prenatal screening.[8 9]

Scarcely any other medical field has produced such conceptual difficulties as the evaluation of prenatal screening. Some screening techniques are risky: two patients are involved; and the decision to terminate a pregnancy is complicated by the possibility of replacement. The benefits of screening have been taken as the costs averted by terminating a pregnancy which might have resulted in an impaired child. Legitimate though this may be where the exchequer costs of care are of prime concern, the real benefits of screening are found in the value of reassurance and the reduction of anxiety in mothers. In principle the QALY approach is best suited to the appraisal of this type of therapy, but a fully satisfactory evaluation of these subtler effects requires far more sensitive measures of the quality of life than are currently available.

More generally, paediatricians may wonder whether existing measures of the quality of life are appropriate for their specialties. Most measures were designed for adults and do not take account of the costs and benefits of treatment to families. All illness imposes costs on families, but in paediatrics the decision to treat or not to treat can have profound pecuniary and nonpecuniary implications for parents and siblings as well as for the health services.

These strong interconnections between the welfare of the patient and the family complicate judgments on whose opinions should count in the allocation of care for children. The Oregon method attempts to reach a social consensus which could overrule the views of parents and in some circumstances this might be morally defensible. On the other hand, it might be thought that the views of parents should carry special weight, especially since in one study of neonatal intensive care parents judged some 'states of health' to be worse than death.[4]

The Oregon approach values alternative states of health by consulting public opinion. It was reported that the Oregon public gives high priority to preventive medicine, accident and emergency services, life saving therapies for chronic diseases, drug addiction and maternity care. Intuition suggests that in the UK there is a widespread sentiment in favour of the treatment of children over the elderly, and that most paediatric treatments would receive a relatively high priority, but no comprehensive opinion poll has been conducted.

Some qualms

An immediate objection to a priority system based on QALYs is that it offends against principles of equity within the NHS. This objection is weakened by the difficulties which exist in demonstrating that the NHS has reduced inequalities in health status. Nevertheless, a 70 year old patient who is denied heart surgery, and may never have used the NHS previously, is bound to reflect that he would have fared better under a private insurance system.

The Oregon system is also vulnerable on operational grounds. QALYs were always intended to be operational, but most health economists thought of the QALY method as an organising principle which would slowly gain acceptability as problems of measurement became better understood. Few economists would have proposed a full scale application of allocation by QALYs if only because the data requirements are so large.

A fully operational scheme requires the evaluation of all medical therapies and a large number of inputs to those treatments, such as alternatives in diagnostic techniques. Consideration should also be given to treatments which are not offered currently, perhaps because they are regarded as medically inefficient. It is entirely possible, for instance, that cheap drugs with rare side effects could be more efficient in QALY terms than more expensive safer drugs.

Many other options should also be considered. These include choices between preventive and curative medicine, hospital and community care, and alternative locations of care.

Health care evaluation must be a continuous process. Costs and technology change constantly, and the variables which enter into the QALY calculations can be altered by changes in staffing levels, management practices, and 'learning by doing'. To meet these data requirements even partially would require a huge input from clinicians, economists, accountants, and other health care workers. Allocative mechanisms currently in use may be inefficient and difficult to defend but at least they are administratively parsimonious.

Even if operational problems could be solved at a cost commensurate with the benefits of the Oregon scheme, other objections would remain. Estimates of the costs of QALYs gained are averages derived from statistical samples of patients. On this basis, treatments for infertility and neonatal intensive care for infants of very low birth weight were singled out in the television programme as therapies which might not be offered in Oregon. The treatments were said to be expensive and the outcomes uncertain, so on average the cost of a QALY is likely to be relatively high.

Averages may not be a good guide to the cost of gaining a QALY for a particular patient. It is suggested that neonatal intensive care might not be viable for infants of birth weight less than 1000 g, but in complex treatment, wide variance will be found in the cost of a QALY, and some cheap QALYs will be obtainable even in the lowest birthweight ranges. Studies of several cohorts of infants in the Mersey region have found no simple relation between birth weight and the cost of care[10] and no statistical justification for the selection of 1000 g as the cut off point below which treatment was not justified.[11]

It follows that rules based on average experience which threaten to replace clinical discretion may be inefficient. Clinicians treat individual patients rather than statistical averages and both medical and economic concepts of efficiency require treatment to be continued to the point where the extra (marginal) cost equals the extra (marginal) expected benefits. In practice, marginal costs and benefits are difficult to measure but the principle is clear: if the benefits to be expected from spending an extra pound on a patient are valued at more than one pound, the treatment should proceed. It is interesting that the medical method of treatment by which patients are monitored, day by day, or hour by hour, conforms much more closely to this fundamental economic principle than does the application of a rule based on average QALYs.

The greatest fear is that a rigidly applied system of priorities, based on highly imperfect estimates of the cost of gaining a QALY, would turn from a economist's dream into a Stalinist nightmare. Eastern European experiments in planning failed because it was difficult to replace private initiative with rules. In the NHS, clinical freedom to pursue the best interests of individual patients may have to be constrained in the wider interests of society, but any such constraints must be broadly acceptable to the profession and the public. The Oregon experiment is audacious and has a logic which some will find compelling, but a full scale application of this approach seems premature in the present state of the art of health care evaluation.

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Paediatric home care in the 1990s

D Lessing, M A Tatman

Home care is not a new concept. Before the emergence of scientific medicine the rich were cared for at home by their physicians, and hospitals originated as charitable institutions in which the destitute, as much as the sick, were cared for.

A shift in the emphasis of hospital work from the social to the scientific began before the industrial revolution, and has accelerated during the era of the NHS. The expansion of medical technology has made the hospital a place for the application of rapid and sophisticated methods of medical management to the acutely ill. Priorities are efficiency, cost effectiveness, and fast turnover of patients. Though lengths of stay have been reduced, admission rates have risen.[1] In inner city areas hospitals have become sources of primary care for their catchment populations, thereby usurping the role of the general practitioner.[2] It is against this background that home care has developed.

Emergence of home care in Britain

In October 1989 the King's Fund produced a document entitled *Hospital at Home: The Coming Revolution*,[3] which highlighted the increasing attention being paid to the concept of caring for seriously ill people at home by offering them intensive domiciliary support to avoid admission to hospital or at least to keep their stay as short as possible. Various factors may be responsible for this revival including the high cost of inpatient hospital care, the development of new techniques that make sophisticated home care feasible, patients' preference for home services, and the belief that outcomes may be improved by home nursing. Many 'hospital at home' schemes have been particularly concerned with the requirements of the elderly but paediatric schemes are now becoming more widely accepted.

The first paediatric schemes to be set up were in Rotherham in 1948,[4] and in Birmingham in 1954.[5] In the same year a home care service involving paediatricians as well as children's nurses was set up based at St Mary's Hospital, London.[6]

For more than 20 years there was little development of paediatric home care schemes; there were five such schemes in Britain in 1970 and seven in 1980, yet by 1988 there were 28 general home care schemes in operation[7] and in 1991 there are 46, together with 30 specialist schemes.[8] The specialist schemes care for neonates and children with specific conditions such as cancer and diabetes.

Home care in the United States

In the United States, cost containment and the system of prospective payment for hospital care based on diagnosis related groups has resulted in a strong incentive for hospitals to discharge their patients 'quicker and sicker'.[9] This has created an enormous demand for home health care. Services provided for children include apnoea monitoring, parenteral nutrition, intravenous medication, chemotherapy, and respiratory treatment.[10]

Home care is big business in the United States, and the increasing availability of technology designed to be used in the home both facilitates the work of home care and provides a commodity for the market. Despite the absence of any proof that apnoea monitoring reduces the risk of sudden infant death, sales of apnoea monitors reached $15 million in 1988.[10]

Functions of home care

The services of a home care team include:

- Direct services such as changing dressings, giving drugs including chemotherapy, tracheostomy care, general nursing care, and counselling.
- Monitoring of the patient and the effects of treatment by physical examination and the obtaining of laboratory specimens.
- Education of the family and patient, teaching therapeutic programmes, and enabling parents to care for their children.
- Coordinating services with hospital, general practitioner, and community.
- Patient advocacy.

The home care team is therefore multidisciplinary. The core team at St Mary's consists of a paediatrician, nurses trained in paediatrics, and a part time social worker. Physiotherapists and child psychiatrists are available to treat selected cases.

Children who particularly benefit from a home care programme are those with complex problems who need a coordinated multidisciplinary approach, those whose condition has not been stabilised in hospital, and children who are at risk in a hospital environment such as those who are immunocompromised. The burden placed on the families of such children may be minimised by regular and supportive home visiting.

The role of a home care team is to enable parents to take increasing responsibility for the care of their children and to be able to initiate services when required. Home visits may initially be frequent, but as the parents gain confidence the number of visits can be reduced. Many families seem more receptive to care and education when it is provided at home, and repeated visiting permits teaching of the care of the child in the context of daily needs. Home visiting seems to build up trust between the family and professional by reducing barriers that may be present in hospital. Dealing with

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children in a family requires recognition that the paediatrician does not have ultimate control.

Home care in the new health service

The changes currently taking place in the health service are of direct importance to home care.

The 'purchaser' function of the district health authority will mean that there is a shift from the management of services to assessment of how best to meet the health needs of their populations.[11]

One of the principal effects of this is to bring to light the existing competition for funding between service providers all of whom are now contractors. This is not only between alternative sources of the same service, but also among the different elements of the health service that exist within a district.

Paediatric home care is likely to be competing for funding with health visiting and district nursing within a community services budget that is itself competing with the acute unit. The information that is most needed by the district health authority will therefore concern the extent to which home care can compete with acute paediatric care and other children's services for the workload. In particular, estimates of inpatient days saved and reductions in costs will be important.

Furthermore, fund holding general practitioners may wish to manage children themselves at home with the help of home care nurses, rather than refer them for hospital admission.

There will be a need for the responsibilities of home care to be clarified together with those of the general practitioner and the hospital paediatrician. Who should be responsible for assessing a child who has been discharged from hospital and then deteriorates at home?

Importance of evaluation

It is possible that increasing financial constraints on the health service may lead to children being discharged earlier from hospital. This will create an increasing demand for home care services. It is therefore important to gather information about the costs and effects of such services and the burdens that they may impose on the family caring for the child.

The objectives of home care services must be clearly defined in such a way that they may be measured. A service with objectives that are hard to measure is vulnerable to competition for funding from services which provide easily quantifiable outputs. The surgical specialties can readily provide information on their inputs and outputs from waiting lists and records of operations carried out. Such information has a strong influence on decision making, though it may not be a valid measure of need or of outcome.

Evaluation must therefore consider the following questions:

- How many children can be kept at home instead of being admitted to hospital?
- Can children be discharged earlier than would otherwise have been feasible?
- What are the comparative costs of home care and of keeping children in hospital?
- Is consumer satisfaction increased?

Donabedian stated that 'achieving and producing health and satisfaction, as defined for its individual members by a particular society or subculture, is the ultimate validator of quality of care'.[12] Studies of consumer satisfaction with medical care have become an important component of health service research. Consumers are becoming more demanding about the type of care they receive and providers are becoming more attentive to their concerns. The district health authorities will be expected to carry out surveys to find out what patients, general practitioners, and the community think of the quality of services provided.[11]

Not only is patient satisfaction an integral part of quality of care, but patients who are more satisfied and hence more concerned in their own care will be more likely to comply with treatment regimens and may thus have better outcomes.[13]

Approaches to evaluation of home care

The scheme was set up in Rotherham because of a high infant mortality rate that was thought to be the result of cross infection in hospital.[3] After three years the infant mortality rate had been halved. This might, however, be explained by other factors.

In a study carried out in the Bronx, children with chronic disorders were randomised to receive either home care or standard care.[14] Interviews were carried out before and six months and one year after the test. The findings were that the intervention group had significantly greater benefits in two and possibly three important areas: satisfaction with care, the child's psychological adjustment, and (possibly) the mother's mental health.

Mitchell *et al* described a randomised controlled trial of an educational programme at home.[15] Children who had been discharged after admission to hospital for asthma were randomised into 'intervention' and 'control' groups. The intervention group were visited for six months by a nurse whose role was to teach and advise the family. A number of outcomes were examined including use of drugs, parental knowledge, and readmissions to hospital. The only difference was that there were more readmissions to hospital among children who had received the intervention.

A non-randomised controlled trial in Boston, compared home and hospital intravenous antibiotic treatment for infectious exacerbations of cystic fibrosis.[16] There were no significant differences in the rate of recovery of respiratory function in either group. Charges billed to the home care group were 60% of those for hospital care. This was a simple method for estimating cost effectiveness—the cost of alternative ways of obtaining the same outcome. Costs of a service comprise direct costs such as money spent by patients and health services, and indirect costs such as lost earnings or time spent by relatives caring for the patient.

The money saved by earlier discharge from hospital is termed a marginal saving. The most expensive care is usually concentrated at the beginning of a hospital admission, so that the marginal saving is less than the average cost of an inpatient day. If expenditure on overheads is unchanged the marginal saving may be as little as 10% of the average cost.[3]

Even if marginal savings are small the freeing of beds by early discharge of children will enable a greater throughput of patients. Under the present system this is a disadvantage as it entails further expense. In the future hospitals will be paid for each case and the advantages of early discharge will be seen not in marginal savings, but in the extra income generated by providing more care with the same facilities.[17]

Paediatricians considering establishing a home care service will need to weigh the potential benefits against the cost. Bergman *et al* argued that 'a home care programme should not be looked upon as a means of saving existing hospital money, but rather as providing a new type of comprehensive service.'[18] There is a need for further evaluation to assess the costs and benefits of home care services.

In 1968 Shrand foresaw that home care would 'realise its full potential in providing a hospital without walls extending into the community'.[19] In the 1990s home care will be increasingly important within the integrated child health services.

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Penicillin resistant meningococci

I have always felt uneasy about relying on penicillin alone in the treatment of meningitis even when Gram negative diplococci are reported early on. Most of my patients get chloramphenicol, or more recently a cephalosporin, added to the penicillin—the main reason being that it is not unknown for on call bacteriology to be wrong and in meningitis you don't take chances. Recent evidence about the emergence of strains of *Neisseria meningitidis* relatively resistant to penicillin I feel add support to this policy.[1–3]

In Leeds an 18 year old man with meningococcal meningitis relapsed on day 5 of treatment with penicillin but recovered quickly on chloramphenicol.[1]

Penicillin insensitive meningococci have been reported from Spain, Britain, South Africa, and most recently from Cananda.[4] A report from Manchester showed reduced susceptibility to penicillin to have been constant at about 3 or 4% of isolates between 1987 and 1989. In Toronto the figure was 2·4% in 1989 and 7·4% in 1990.[4]

Obviously we can no longer rely on *N meningitidis* being fully sensitive to penicillin. Either higher doses of penicillin or an alternative antibiotic may be needed. 'Belt and braces' is not a bad principle in the treatment of meningitis, at least initially.

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INTERNATIONAL COMPARISONS

Health care of American children

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The use of infant mortality rates, perinatal mortality rates, and other population measures as the basis for comparison of child health trends in different countries is familiar to us all. Differences in rate are usually attributed largely to variations in nutrition, housing, and public health policies. Though socioeconomic factors are undoubtedly important as determinants of child health, the provision, efficacy, and uptake of health services cannot be dismissed as of little significance. Perhaps national differences in the delivery of health care have not attracted much attention because most countries are preoccupied with their internal arrangements and tend to believe that other systems are unsuitable or not applicable to their own situation. Concern about the deteriorating position of the USA vis-à-vis some other developed countries in such areas as immunisation against contagious diseases, care of acute illness as reflected in postneonatal infant mortality rates, unintentional injury, and care of children with special health needs, however, stimulated the American Academy of Pediatrics (AAP) to probe deeply into the reasons for the relatively poor American performance and to invite comparisons from other developed countries (Canada, England and Wales, France, Norway, and the Netherlands). The resultant conference and its published report documented the necessity for the USA to address the needs of all its children, to establish priorities, and to set goals.[1]

In all four of the areas of child health examined in the AAP report, America compared unfavourably with the other countries. Thus deaths from accidents and postneonatal infant mortality rates were both worse than in Europe and services for children with special health needs were not so widely accessible. The incidence of contagious diseases, still a major cause of death in developing countries, declined precipitously in the USA during the past half century because of a successful immunisation policy. However, rates of routine immunisation of preschool children are now falling and unvaccinated children are increasingly at risk. There is no readily identifiable reason for this, though inadequate health insurance and the rising cost of vaccines are thought to play a part.

Immunisation rates of 55 to 65% for selected diseases now compare with rates of 80 to 100% in certain northern European countries and 76 to 87% in England and Wales. The rates in the USA vary widely between ethnic groups but even the highest rates among white Americans are well below those of the European countries. In England and Wales, despite a relatively favourable situation, national immunisation rates of over 90% have not yet been achieved and there is considerable regional and social variation, so sustained effort and continuing vigilance are essential both in the UK and in the USA.

With all the ideas advanced to explain these and other national differences, it is important to bear in mind the diversity of provision within the USA. All the other countries considered have more uniformity in the organisation of services because they have greater unity of political structure, with a substantial degree of central control of policies and performance. In the USA, where sizable autonomy is exercised by each state, there is a much wider range of service quality, from the excellent to the poor, and national figures reflect this variety. Statistics do not tell the whole story, for the greater the degree of control the larger the potentiality for better figures but the less the opportunity for personal choice. Too ardent a devotion to improving statistics may therefore sometimes result in unacceptable restriction of individual freedom, as sometimes appears to be a risk in the maternity services. Nevertheless, there seems no doubt that the relatively poor figures in the USA are the result of fragmentation and duplication of services with too many gaps, of economic disincentives, and of failure to act decisively in such matters as traffic regulations and firearms control.

Some of the agonising of the Americans may be misplaced. For example, the President of the AAP, Birt Harvey, deplores the tendency in the USA to look at children as chattels of their families, while other developed countries consider their children to be a national resource. Would that this were true of the UK, which is far from being a childcaring society! Harvey is disproportionately hard on the record in the USA when he compares child abusing Americans with the European peoples who 'tend to treasure and care for all children'. Child abuse statistics from Europe do not bear out this idyllic view and indeed Henry Kempe always said that child abuse would be found in every country if only people looked for it.

Comparison of the USA with a group of other developed countries tends to lump the latter together, obscuring differences between them and creating an artificial 'us and them' antithesis. Thus, for example, the laxity of laws on drunk driving is said to illustrate lower standards in the USA, yet these laws, extremely strict in Scandinavia for many years, have only recently been tightened up in the UK, which still lags behind other European countries.

Canada might be thought to afford the closest comparison with the USA, because they share a North American history and culture. The

Canadian health care system is a compromise between 'fee for service' and socalled 'socialised medicine' and the balance is claimed to be remarkably successful. In Canada, though responsibility for health is shared between federal and provincial governments, the Federal Department of National Health and Welfare serves, in the words of Ivan Pless, as 'the spiritual guardian of the integrity of Canada's health services'. The principle of a two class system of health care, one for the rich and another for the poor, does not exist anywhere in Canada. Whereas in the UK families are means tested to establish their entitlement to milk and vitamins, help with travelling costs to hospital and other benefits, in Canada no demeaning test determines the availability of health care. In that country, they really believe that equitable access to medical care is essential to the integrity of a fair and just society, whereas the USA fails to guarantee adequate care for all children because eligibility and benefits are so variable.[2]

England and Wales, along with the rest of the UK, have had a National Health Service for over 40 years, originally based on the principle of free and equal access to health care for all but presently in process of change towards a compromise system between a state service and free enterprise.[3] The effects on child health of the changes being introduced are imponderable but among fears expressed are that children with chronic disease or disability will be at a disadvantage because the cost of their continuing care will weigh too heavily on the budgets of family doctors. Moreover, there is incongruity between a system of buying and selling hospital services on a contractual basis and the concept of a single planned hospital service for children, whose needs are so different from those of adults, and there is enormous potential for divisive duplication.[4] On a more optimistic note, the adverse effects of mercenary policies and persistent underfunding may be offset by effective integration of the child health services in each region and district, linking together preventive services, acute services, and services for the chronically disabled or ill child. Such coordination of health programmes to meet children's needs was advocated by the Court committee[5] but has not yet been fully implemented.[6] Attempts to improve resource management and medical audit are laudable but might more sensibly have been undertaken in the context of a free and universally available service. In a system of bargaining for services from various separate providers,[7] a danger is that administration, already time consuming, becomes an end in itself and much more expensive than the cost of administering the present health service. In such circumstances, despite government protestations that the patient comes first, the real needs of children tend to be lost sight of amid the havoc that competition brings to health care.[8] There is thus a tension between conflicting philosophies in the health service in the UK and only time will tell whether or not the new patterns of child health care will be to the greater benefit of children and their families.

Every system of child health care has its strengths and weaknesses. For example, the strengths of the French system are the universal health record (carnet de santé), recording specific information at selected ages, and the specialised Centres for Early Medico-Social Action. Weaknesses are the shortage of staff and resources in the school health service and unevenness in availability of some social supports. Similar strengths and weaknesses could be pointed out for all the national health systems considered in the AAP report. The willingness of Americans to expose their deficiencies and to indulge in honest and frank soul searching is admirable, for many countries in the world have neither the courage to do so nor the hard data from which to draw conclusions.

The balance between individual freedom and community aims is complex and will vary between countries and between states in a federal system, depending on such variables as historical development, political philosophies, national temperament, and cultural patterns. Community aims lay great store on protecting the wellbeing and security of its weaker members and this necessarily means curbing individual rights in some degree. For example, in most countries, though apparently not in America, the safeguarding of a woman's employment during and after pregnancy involves imposing conditions on employers. Children are vulnerable and cannot speak for themselves, so that the scales should be tilted from personal liberty towards community responsibility when child health services are being considered. A fundamental characteristic of the American health system is the freedom of the individual to choose, wisely or unwisely. However, the Canadian experience provides cogent reasons why the USA should move towards a more planned and regulated system of universal health care and this recommendation is made in the AAP report, which observes that a decade of trying market systems based on individual responsibility shows that these approaches have not worked. It is ironic, therefore, that at the same time the UK is moving towards a competitive market system, especially as the Canadian example suggests that deregulation and competition tend to increase costs and diminish the quality of health care. Moreover, the burgeoning of private medicine is unlikely to improve child health, for in the French system, which combines public and private components, there is a notable weakness of information for statistical analysis coming from the private sector—a salutory observation for those advocating a move towards private care.

The difficulties of providing for minority populations, especially underprivileged and migrant groups, are evident in all countries and are especially emphasised by Manciaux.[9] Disparity in health between socioeconomic groups within a country is often of greater importance than small differences between total population rates for comparable nations. Thus there is evidence that in France the differential in infant mortality between the social extremes, while still too wide, is narrowing. By contrast, in New York City the neonatal and infant mortality rates in disadvantaged urban communities have risen dramatically in the past few years.[10] In the UK, where some four million children live in poverty, the health gap between the affluent and the poor is known to be widening. Clearly both the USA and the UK should study the variations in rates between different sections of their own child populations if the aim is to improve overall statistics. Such scrutiny will demand action and action costs money: no extra money means no resources for these children or their families.

Relative national costs of health care were not closely examined in the AAP report but it was observed that the per capita health bill in the USA (over 11% of gross national product) may be too high in relation to the services provided and the results achieved. It is 41% higher than Canada's expenditure and 85% more than France's, but the fact that it is 171% more than Britain's should give us food for thought about our priorities in the allocation of national resources. Even if total financial provision for the health service were to be increased, there is no certainty that children would receive the priority that such a precious national asset should demand. As Sverre Lie says, speaking of the Norwegian health services, 'for children there will be a constant fight to retain a reasonable share of the cake' and this is true for all countries and all systems.

The AAP report concludes that the USA must change its philosophy about social welfare and about looking after children. Steps are already being taken towards improving the health and welfare of all children but it is conceded that the end of this road will not be reached for many years. Nevertheless, despite all the self criticism and heart searching, the reader cannot but reflect how fortunate is a child living in the USA, or indeed in any of the countries considered, in comparison with a child born in one of many countries in Asia, Africa, or South America, whose heritage is destitution and famine, whose quality of life is often grim, and whose fate is likely to be malnutrition, disease, and all too often early death.

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Campylobacter jejuni and Guillain-Barré syndrome

Although it has long been known as postinfective polyneuritis it is unusual to demonstrate a specific infectious aetiology in Guillain-Barré syndrome. Recently, however, there have been several reports linking the syndrome with *Campylobacter jejuni*. A paper from Japan (Shigekazu Kuroki and colleagues, *The Pediatric Infectious Disease Journal* 1991;**10**:149–51) reports on 11 patients aged 7–14 years with Guillain-Barré syndrome seen over a five year period. Stool culture was performed in eight of them and *C jejuni* isolated in seven of whom five had had diarrhoea or abdominal pain or both. Serotyping was done in four cases and all four had *C jejuni* type 19 a serotype previously found in only 1·7% of cases of *C jejuni* enteritis in Japan. In a previous survey *C jejuni* was isolated from the stools in 1·7% of healthy children. The authors found no evidence to support a previous suggestion that Guillain-Barré syndrome might be more severe when associated with *C jejuni* infection.

A stool culture should be included in the diagnostic work up of children with Guillain-Barré syndrome.

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Acta Paediatrica Scandinavica

Acta Paediatrica Scandinavica is a well established journal of high repute and recognition. It is now in its 80th volume. It is a monthly journal, but also produces supplements of considerable expertise, which are a useful adjunct to the journal's overall annual volume.

The journal contains a mixture of original articles, short communications, case reports of supposed interest and also an editorial comment where one paper per journal is subject to editorial review. This I find a very useful aspect of the journal as it often tackles papers which raise controversial points and discusses them in a dispassionate fashion. The book review in December 1990 was of little value considering the size of the book that was reviewed. Announcements and diaries in journals, I have never found useful.

I find the journal extremely useful. It seems to me to fill the gap between a journal such as *Archives of Disease in Childhood* and *Pediatric Research,* which is very much laboratory or bench based research. *Acta Paediatrica Scandinavica* seems to marry the two disciplines really rather well. I also find it rather more readable and understandable than *Pediatric Research* as the papers tend to be written very much more with the paediatric world in mind rather than the pure scientist. The neonatal population are a captive audience, akin to the laboratory rat, and in common with many other journals neonatology papers are over represented in the December issue compared with the relative importance of neonatology throughout all of paediatrics.

In my own area of interest, however, the papers on diabetes that happened to be published in the December issue exemplify well the combination of virtual laboratory research with regard to sodium and lithium transport and more clinically based research with the psychological report of personality and metabolic control. I feel the inclusion of short communications is an excellent idea. A short research project can be included within this area and allows rapid publication of research projects which are not enormous in their scope.

I remain consistently sceptical, however, about the use of case reports. In order to gain publication the case must be extraordinarily rare, and it seems to me that the only purpose of this is to expand the authors' lists of publications rather than lend useful and practical knowledge to the paediatric fraternity. This criticism, however, is not peculiar to *Acta Paediatrica Scandinavica.*

I enjoy reading the journal and would strongly recommend paediatric departments to take this journal which is relatively cheap compared with many of its European counterparts.

STEPHEN J ROSE

Archives of Disease in Childhood 1991; **66:** 1001–1004

LETTERS TO THE EDITOR

Respiratory rate and pneumonia in infancy

SIR,—Dr Berman *et al* have presented an interesting and comprehensive paper about the use of respiratory rate in infants in the diagnosis of pneumonia.[1] This is an important topic because counting respiratory rate is a critical aspect of the World Health Organisation acute respiratory illness programme.

One of the difficulties has been that the normal range of respiratory rate had not previously been defined. The object of our paper was to define the normal range of respiratory rate in infants when they were awake.[2] Berman *et al* suggested that our results (mean (SD) 61 (18)/minute) were too high because they do not compare with studies using electronic monitoring. Unfortunately, electronic monitoring is not a satisfactory gold standard for respiratory rate because studies in awake babies have movement artefact and the study of sleeping babies is not appropriate for routine clinical practice. Our range of respiratory rate for sleeping babies was similar to those in the published literature (42 (12)/minute).

They suggest that the use of a stethoscope or a hand on the chest for counting the respiratory rate in our study may have stimulated the infants to breathe faster than normal. Their own studies suggest this can result in a respiratory rate 14 breaths/minute higher than that obtained by observation. This may be possible, although it was not our observation. We used this technique simply because we found it very difficult to count respiratory rate by observation and wanted to use a technique that could easily be used in all babies regardless of their state. It was our experience that respiratory rate could be counted by observation accurately in sleeping or ill babies because they lie still and often have increased respiratory effort. It was surprisingly difficult in lively healthy babies because they move approximately once a second and also breathe shallowly and irregularly.

Berman *et al* compare our data with a study in which respiratory rate was counted by observation in a community in Peru. Unfortunately, even that data can not be considered to represent the respiratory rate range of normal infants because the children were selected for the study only if they had a cough.

Unfortunately, the authors make a common statistical mistake when calculating sensitivity, specificity, and predictive values for pneumonia using respiratory rate above or below 50 or 60 breaths/minute. Their data were collected only from selected children seen in hospital. In their Denver study the infants were only seen if they had a cough or congestion and in the Vellore study the infants presented with a runny nose or cough.

The authors had no data from normal infants. Sensitivity, specificity, and predictive values are accurate only for the populations from which the data were derived and cannot be extrapolated to infants in the community. Even using this selected data the sensitivity of a respiratory rate of 60 or more for lower respiratory infection was only 63% in Denver and 58% in Vellore. To be a useful screening test for pneumonia, respiratory rate measurement must have a much higher sensitivity.

Before it can be claimed that respiratory rate is a useful screening test for pneumonia data must be presented using a simple technique of proved accuracy and repeatability from children with pneumonia and normal children in the communities where it will be used.

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1 Berman S, Simoes E, Lanata C. Respiratory rate and pneumonia in infancy. *Arch Dis Child* 1991;66:81–3.
2 Morley CJ, Thornton AJ, Fowler MA, *et al.* Respiratory rate and severity of illness in babies under 6 months old. *Arch Dis Child* 1990;65:834–7.

Drs Berman and Simoes comment:

We appreciate the opportunity to respond to Dr Morley's comments on our annotation. The issue of the usefulness of simple clinical signs to identify pneumonia is important and we agree that it is necessary to document the range of respiratory rate counts in infants with and without acute respiratory infections. Interpretation of studies is impaired by the use of different counting methods. Unfortunately there is no counting method that can be considered a gold standard. It is possible that differences in respiratory rates reported in studies may partially reflect the different methods used to obtain them. Our own study comparing simultaneous counts obtained by observation versus electronic pneumogram tracing documents differences between these methods.[1] Our annotation pointed out that counting with a stethoscope or by placing a hand on the abdomen may itself result in differences compared with obtaining counts by other methods. The use of a 15 second counting interval would also increase any consistent difference by a fourfold factor. We agree with Dr Morley that counting respiratory rates in very active 'lively' infants is difficult regardless of the counting method. Our recently completed study corroborates this finding.

The World Health Organisation (WHO) chose to develop respiratory rate thresholds based on data obtained using 60 second observed counts. This choice was made for operational reasons, based on the need to train community health workers to count respiratory rates without using a stethoscope.

The WHO respiratory rate thresholds have been designed to be used on subjects who have respiratory symptoms of cough or coryza. The case management guidelines are not relevant for healthy infants and children without respiratory symptoms. It is for this reason that sensitivity, specificity, and predictive value should be calculated on populations with respiratory symptoms. The predictive value of the respiratory rate threshold for pneumonia will vary with the prevalence of the pneumonia in the population with respiratory symptoms. It was not our intention to generalise sensitivity, specificity, and predictive value to the total population of children with and without respiratory symptoms.

We agree that the sensitivity and specificity of the WHO respiratory rate threshold applied to infants under 2 months of age is not as good as that in older infants and children. Further research is needed to evaluate the usefulness of the threshold in association with other clinical signs to diagnose pneumonia in that age group. Studies are underway in the Gambia and the Philippines to clarify these issues.

1 Simoes EAF, Roark R, Berman S, Esler LL, Murphy J. Respiratory rate: measurement of variability over time and accuracy at different counting periods. *Arch Dis Child* 1991 (in press).

Diagnosis of pneumothorax by echocardiography

SIR,—Over the last 18 months we have performed frequent echocardiograms on ventilated neonates as part of a study on haemodynamics.[1] Pneumothorax is common in this setting. We report three cases where pneumothorax was first suspected on echocardiography.

Case reports

CASE 1

This infant, born at 41 weeks' gestation weighing 2370 g, was ventilated after birth asphyxia and meconium aspiration. A chest *x* ray picture at 4 hours showed no air leak. At 22 hours the heart was difficult to see echocardiographically and was best seen from the right sternal edge. There was no clinical deterioration. Transillumination was negative. A further chest *x* ray picture showed a small left pneumothorax which was managed conservatively. Five hours later, radiography showed no air leak and echocardiographically the heart was easily seen and normally positioned.

CASE 2

This infant, born at 25 weeks' gestation weighing 785 g, was ventilated for hyaline membrane disease. There was no air leak on a chest *x* ray picture at 4 hours. At 16 hours, on echocardiography, the heart was difficult to see and displaced to the right. Transcutaneous carbon dioxide had risen from 4·5 to 6·9 kPa over the previous half hour. Transillumination showed left tension pneumothorax. After drainage, the heart was no longer displaced on echocardiography.

CASE 3

This infant, born at 27 weeks' gestation weighing 1040 g, was ventilated for hyaline membrane disease and birth asphyxia. A chest *x* ray picture at 10 hours showed no air leak. Echocardiography at 14 and 36 hours showed poor myocardial function. From 48 to 52 hours systolic blood pressure fell from 40 mm Hg to 32 mm Hg despite support. At 52 hours the heart was difficult to see echocardiographically but was displaced to the left with the apex tilted cranially. Transillumination showed right tension pneumothorax. After drainage the blood pressure rose to 58 mm Hg; echocardiography showed an easily seen, normally positioned heart.

The heart is normally easy to see echocardiographically in the neonate ventilated for hyaline membrane disease. In these three cases the heart was difficult to see from the left sternal edge, and was displaced laterally, away from the air leak; this was presumably due to a combination of mediastinal shift and interposing air, which is impervious to ultrasound.

Unilateral pulmonary interstitial emphysema has mimicked these findings, hyperinflated lung lying in front of the heart. With other causes of mediastinal shift the heart should be easily seen unless there is air in front of it; in diaphragmatic hernia the heart should be visible in its displaced position[2] until bowel gas accumulates.

Ultrasound is therefore a new technique to diagnose pneumothorax, but it is clearly not the best, and any suspicion should be confirmed using conventional methods before treatment. Nevertheless, pneumothorax can be a catastrophic complication of hyaline membrane disease, and those performing echocardiography on sick, ventilated neonates should be aware of this, so if the heart is difficult to visualise, or is laterally displaced, the attending clinicians can be informed immediately.

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Dr J Skinner is supported by the National Heart Research Fund.

1 Skinner JR, Hunter S, Hey EN. Pulmonary artery pressure in hyaline membrane disease. *Pediatr Res* 1990;28:286.
2 Crawford DC, Wright VM, Drake DP, Allan LD. Fetal diaphragmatic hernia: the value of fetal echocardiography in the prediction of postnatal outcome. *Br J Obstet Gynaecol* 1989; 96:705–10.

Fluconazole in neonatal disseminated candidiasis

Sir,—We report the case of an infant, born at 28 weeks' gestation weighing 900 g, who on the 22nd day of life had thrombocytopenia and leukocytosis. Urine and blood cultures yielded *Candida albicans*. Amphotericin B was raised to 1·0 mg/kg/day by day 4 and on day 5, flucytosine 25 mg/kg every six hours was added and a broviac catheter inserted. Peripheral and central blood cultures on the 7th, 14th, and 18th days of treatment with amphotericin B continued to yield *C albicans*, and cultures of abscesses on the forehead and arm yielded *C albicans* on day 18. Ultrasound of the kidneys, head, and abdomen as well as an ophthalmologic evaluation, gallium scan, and culture of the cerebrospinal fluid were negative. Amphotericin B and flucytosine were discontinued after 18 and 12 days, respectively. The catheter was removed and intravenous fluconazole (6 mg/kg/day) initiated.[1] The catheter was replaced on day 4 of fluconazole. On day 5 of fluconazole peripheral and central blood cultures were negative for *C albicans*. Fluconazole was discontinued after 20 days with cultures remaining negative during four months of follow up.

Fluconazole serum concentrations three hours after the infusion and before the next dose on day 7 of treatment were 10·30 and 6·98 μg/ml. Amphotericin B concentrations were 0·21 μg/ml on day 14 of treatment and 0·12 μg/ml 30 days after discontinuation. A first order, one compartment model[2] resulted in the following pharmacokinetic parameters for fluconazole:

$$t_{½}\beta = 37{\cdot}4 \text{ hours, } aV_d = 1{\cdot}2 \text{ l/kg,}$$
$$CL = 0{\cdot}02 \text{ l/kg/hour.}$$

(Where $t_{½}\beta$ is terminal elimination half life, aV_d is the apparent volume of distribution, and CL is clearance.) This indicates a larger aV_d and a longer $t_{½}\beta$ as compared with adults (0·7 (0·06) l/kg and 22 (3·5) hours).[3]

The activities of four antifungal drugs against the isolate of *C albicans* from this patient are indicated in the table.[4] These results do not necessarily reflect therapeutic efficacy. Because of the presence of amphotericin B during and after fluconazole, one could speculate that fluconazole and amphotericin B acted synergistically. Other factors may have also helped to eradicate *C albicans*. Further studies of fluconazole's efficacy in immunocompromised adults with invasive fungal disease are needed before studies in neonates are considered.

Minimum inhibitory concentration and minimum lethal concentration of four antifungal drugs (concentrations in μg/ml)

	Amphotericin B	*Fluconazole*	*Itraconazole*	*Schering 39304*
Minimum inhibitory concentration:				
24 hours	<0·01	<1·25	0·02	<0·63
48 hours	<0·29	5·00	0·02	2·50
Minimum lethal concentration:				
24 hours	0·58	>80·00	>10·00	>80·00
48 hours	2·31	>80·00	>10·00	>80·00

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1 Viscoli C, Castagnola E, Corsini M, *et al*. Fluconazole therapy in an underweight infant. *Eur J Clin Microbiol Infect Dis* 1989;8:925–6.
2 Gibaldi M, Perrier D. Pharmacokinetics. 2nd Ed. New York: Marcel Dekker, 1982.
3 Humphrey MJ, Jevons S, Tarbit MH. Pharmacokinetic evaluation of UD-49,858, a metabolically stable triazole antifungal drug, in animals and humans. *Antimicrob Agents Chemother* 1985;28:648–53.
4 Rinaldi MG, Howell AW. Antifungal and antimycotic laboratory evaluation. In: Wentworth BB, ed. *Diagnostic procedures for mycotic and parasitic infections*. 7th Ed. Washington, DC: American Public Health Association, 1988: 325–56.

Chronic vitamin D overdosage: a reminder

Sir,—After the reported increased incidence of rickets in Asian children in the late 1970s there has been increased awareness of the need for vitamin D supplementation.[1] This is now being recommended by the Department of Health and usually given together with other vitamins in multivitamin preparations. Parents are able to obtain their supply through their local child health clinics under the Welfare Food Scheme.[2] There are also many alternative preparations available without a prescription via other sources, however, including chemists and health shops. Therefore, self medication without professional supervision is a potential danger. Chronic poisoning as a result of inappropriate administration of vitamins is rarely reported now (there has been no case reported in the English language literature in the past 10 years) but we were recently presented with a case of gross hypercalcaemia due to vitamin D overdosage.

A 6 month old Indian boy was admitted with a six day history of vomiting, constipation, and increasing apathy. Examination revealed a drowsy, listless child with signs of 5–10% dehydration. Plasma electrolyte concentrations on admission showed a urea of 7·4 mmol/l, sodium 148 mmol/l, potassium 2·9 mmol/l, and a grossly raised calcium concentration of 5·86 mmol/l.

Subsequent investigations showed an appreciably increased vitamin D concentration (25-hydroxycholecalciferol) at 2226 nmol/l (normal 10–120 nmol/l) and undetectable parathyroid hormone. On close questioning, his parents admitted to administering a compound preparation of vitamins A, C, and D since the age of 4 months, and as he had refused to take these from the dropper, they poured the vitamin into his mouth directly from the bottle instead! They had obtained their vitamin supply from a chemist privately and had received no professional supervision of administration.

The baby was given intravenous fluids for five days and also commenced on a low calcium, low vitamin D diet. He was discharged home on day 12. His calcium returned to normal by day 19 but his vitamin D concentration remained raised for over six months. Follow up at one year showed moderate global developmental delay.

This case illustrates the dangers of unsupervised vitamin supplementation. To prevent further incidents, tighter control over availability of vitamins and improved public awareness of the potential dangers of vitamin overdosage would be helpful. Health professionals should also aim to improve supervision.

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1 Anonymous. Rickets in Asian children. *BMJ* 1979;i:1744.
2 Department of Health and Social Security. *Present day practice in infant feeding*. 3rd Report. London: DHSS, 1988: 35–6, 50.

The paediatric departmental library

Sir,—Dr Clayden is, I fear, somewhat over optimistic when he suggests that we are 'on the brink of a breakthrough in data retrieval' by which we will 'access original articles and learned reviews at the touch of a few buttons . . . so the medical library will pass into the mists of memory'.[1] Clearly this sort of thing is on the horizon. I already spend nearly as much time advising doctors on suitable index terms for searching MEDLINE on compact disc as I do guiding them around the vagaries of the library catalogue. My colleagues and I are, in fact, slowly adapting ourselves to the fact that what we have been doing is storing and retrieving things—books, journals, papers, etc, while what our customers often want is not things, but information. Up till now, however, much of the revolution which is leading to the 'death of the book' and the end of the scientific journal, has consisted of books and journal articles. I wonder if there is any evidence of Caxton or Gutenberg circulating illuminated manuscripts on 'the death of the illuminated manuscript' during the last communications revolution? I also wonder if I would have come across Dr Clayden's opinions if he had circulated them by electronic mail rather than in the form of a journal article.

More seriously, a cause for concern is the common delusion among doctors that because information is going to become available in an electronic form it is somehow going to be 'free'. A quick glance at the organisations currently involved should convince them that this is not the case—DIALOG, which is a subsidiary of the Lockheed Corporation, Pergamon Press, EM-BASE which is owned by Elsevier, and DATA-STAR which is owned by the Swiss Radio Corporation! It seems to me to be much more likely that those hospitals and medical schools which can make a major financial commitment to information systems will end up being much better served than they are at present, but that isolated specialists working in poorer parts of this country, let alone those in Bulgaria or Bangladesh, are going to be considerably more deprived of information than they are at present. Much of the technology already exists, but we do not have the staff to offer it. Brophy tells of a new polytechnic lecturer who had arrived from a commercial research organisation in which he had had a personalised publication bulletin every Monday, with all the documents he ticked in it delivered to his desk by Friday, and a regular visit from his information officer to make sure the document supply was on target.[2] The polytechnic had the technology to do the same, but it had an average of one subject librarian to 1100 readers, and is very unlikely to make the investment in people, as well as in equipment, necessary to take advantage of the technology.

One thing which puzzled me was Dr Clayden's implicit assumption that he is going to retain his functions, and even his title, during the information upheaval he predicts. The 'death of the book' surely implies the abolition of the 'reader in paediatrics'. Even if he changes his title to that of the less euphonious 'VDU-scanner in paediatrics' it seems to me to be much more likely that I will be able to stagger on as a sort of glorified juke-box attendant, but that many of Dr Clayden's functions can be taken over by an Expert System, on the one hand, and by far lower paid counsellors on the other. I hope and expect that he and I will get safely through to retirement all right, but I have doubts about our successors.

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1 Clayden G. The paediatric department library. *Arch Dis Child* 1991;66:370.
2 Brophy P. Organising for change in polytechnic libraries. *Library Association University College and Research Newsletter* 1991;32:10–6.

Dr Clayden comments:

I would support Mr Guha in his defence of the librarians' future. I was merely suggesting in my brief article that the medical library as a place might disappear. The librarians' role of custodians of information systems and experts in retrieval is already taking over from the role of guardians of books. We should not lose sight of the liberation from memorising facts which the accessibility of massive databases is increasingly allowing. I would imagine most patients would prefer their doctor to be expert in *using* data to solve their problems than merely being able to *retrieve* from their own memories the list of facts about a particular illness. Similarly, the librarian who is expert in retrieval of information is more vital than those expert in the effect of climate on the degeneration of books and manuscripts. It is inevitable that I should use a journal to communicate my opinions at this stage as the availability of electronic newsboards has been priced out of the market so far. Similarly, I cannot imagine that Bell attempted to phone his friends about modifications to his invention in the early years either.

I cannot agree in the long term with Mr Guha's anxiety about the developing world. An out of date book is perhaps as dangerous as no book at all. How many remote areas of the world are unable to receive radio broadcasts now? It is therefore easy to foresee the future of sonar powered computers receiving satellite transmitted signals to update databases and expert systems through the world.

On the personal side, I do have to admit to an early fear of books bred (or is it bread) as a result of a degree of dyslexia in childhood. Although the telephone and word processor may be our mode of communication, I welcome the humanity which shines through these contacts by friendly and supportive librarians as much as Mr Guha and I will value that of the future doctors into whose hands we will inevitably fall. Let up hope that their kindness and wisdom are also strengthened by all the powers of science and technology available in that hopefully distant time.

Squatting and urinary tract infection

SIR,—We read with interest the article by Hellström *et al* on the association of urinary symptoms and previous urinary tract infection.[1] Hellström *et al* found urinary tract infection in 15 (37%) of 41 children with squatting. We agree that urinary tract infection is common in children with squatting.[2] In the past 22 months we identified 16 children who presented with squatting at least once per week. The average age at our assessment was 77 months, range 47 to 126 months. There were 15 girls and one boy. The table shows the frequency of chronically holding the urine to the last minute and urinary tract infection in these children. None of the children had encopresis, a gait disturbance, a palpable defect in the lumbosacral spine, or an abnormal neurological examination.

Nine of the 16 children in our series had either a retrograde voiding cystourethrogram taken or cystoscopy performed. Four children had mild vesicoureteric reflux, two had trabeculated bladder (one also had a bladder diverticulum), and one had urethral stenosis. Only two children had normal results on these studies and both of these children had a history of chronically holding the urine to the last minute. Four of the five children who did not hold their urine to the last minute had abnormal results on the studies.

The frequency of chronically holding the urine to the last minute and urinary tract infection in children with squatting (results are number (%) of children)

	Frequency	
	Present series (n=16)	*Hellström et al[1] (n=41)*
Chronic holding of urine	11 (69)	
Urinary tract infection	13 (81)	15 (37)

Hellström *et al* questioned whether symptoms of bladder dysfunction or urinary tract infection come first and whether they develop in a causal relationship. We believe that both urinary tract infection and squatting develop consequent to a number of clinical conditions including chronically holding the urine to the last minute, detrussor sphincter incoordination, or urethral obstruction. Chronically holding the urine to the last minute may become a habit in some children and should be differentiated from children with urgency who do respond promptly to the signals of the need to void. In the former case, parents typically observe these children dancing around, fidgeting, or holding themselves, whereas in the latter case, the sensation comes on suddenly without any warning.

Instructing children to respond promptly to the signals of the need to void, take their time to completely empty the bladder, and void at least every two hours during the day should be part of the treatment plan for children with either urinary tract infection or squatting.

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1 Hellström A, Hanson E, Hansson S, Hjälmås K, Jodal U. Association between urinary symptoms at 7 years old and previous urinary tract infection. *Arch Dis Child* 1991;66:232–4.
2 Robson WLM. Urinary tract infection in children: diagnosis and treatment. *Canadian Family Physician* 1990;36:1597–600.

Gastro-oesophageal reflux and the lung

SIR,—I read with great interest the annotation by Professor Simpson and Dr Hampton about the inter-relationships between respiratory disorders and gastro-oesophageal reflux.[1] The authors did not mention an important group of children in whom respiratory disease and reflux may coexist, namely those with cystic fibrosis. The association between these conditions first came to light 10 years ago when two children were reported in whom gastro-oesophageal reflux disease with recurrent aspiration had been diagnosed, but who were subsequently discovered to have cystic fibrosis.[2] A study from 1985 described a questionnaire survey of 65 patients with cystic fibrosis in whom one quarter reported heartburn and/or regurgitation.[3] A large scale, prospective study of the incidence of reflux in cystic fibrosis patients using intraoesophageal pH monitoring is prevented by ethical considerations, but in a small study of 10 newly diagnosed infants with cystic fibrosis, Dab and Malfroot found significant gastrooesophageal reflux in all 10.[4] These authors suggest that as reflux was documented even in those patients without respiratory symptoms it could not be blamed on chronic cough, and may even represent a primary defect of oesophageal motility in cystic fibrosis. Published data about oesophageal motility in cystic fibrosis are scanty, but there is some evidence that transient relaxations of the lower oesophageal sphincter, which are not accompanied by oesophageal peristalisis, and therefore deemed inappropriate, are commoner in cystic fibrosis patients with gastro-oesophageal reflux than in reflux patients without cystic fibrosis (data presented by F Santamaria *et al* at the 10th International Cystic Fibrosis Congress in Sydney, 1988).

The importance of coughing and physiotherapy in inducing reflux in cystic fibrosis is probably underestimated. The statement by Professor Simpson and Dr Hampton that 'although large swings in intrapleural pressure induced by respiratory efforts have been thought to favour increased gastro-oesophageal reflux, there is little evidence that this actually occurs . . .' may not be true in cystic fibrosis patients. From our knowledge of the pathophysiology of gastro-oesophageal reflux, forced expiration and coughing undertaken during chest physiotherapy may cause a rise in the thoracoabdominal pressure gradient sufficient to overcome the antireflux barrier of the lower oesophageal sphincter, and the antigravity effect of postural drainage in the 'head down' position would also be expected to exacerbate reflux. In a study in 10 young patients with cystic fibrosis investigated with 24 hour oesophageal pH monitoring during which all underwent three periods of chest physiotherapy, eight were found to have pathological reflux, and in six physiotherapy provoked reflux.[5] Although in my experience intraoesophageal pH monitoring is not well tolerated by patients with cystic fibrosis with established pulmonary disease, this is an area which merits further study.

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1 Simpson H, Hampton F. Gastro-oesophageal reflux and the lung. *Arch Dis Child* 1991;**66**: 277–9.
2 Frates RC, Cox KL. Cystic fibrosis mistaken for gastroesophageal reflux with aspiration. *Am J Dis Child* 1981;135:719–20.
3 Scott RB, O'Loughlin EV, Gall DG. Gastroesophageal reflux in patients with cystic fibrosis. *J Pediatr* 1985;**106**:223–7.
4 Dab I, Malfroot A. Gastroesophageal reflux: a primary defect in cystic fibrosis? *Scand J Gastroenterol* 1988;2(suppl 143):125–31.
5 Foster AC, Voyles JB, Murray BL, Murphy SA. Twenty-four hour pH monitoring in children with cystic fibrosis: association of chest physiotherapy to gastroesophageal reflux. *Pediatr Res* 1982;17:218.

Paracetamol suppositories after cardiac surgery

SIR,—We read with interest the article by Hopkins, Underhill, and Booker concerning rectal absorption of paracetamol.[1] We have performed a similar study on 20 children, mean age 3·75 years (range 0·28–10·58 years), giving paracetamol suppositories (Macarthys Laboratories Ltd) when they became feverish, four to six hours after the cessation of cardiopulmonary bypass (11–14 mg/kg body weight). Rectal temperature was monitored continually and plasma paracetamol concentrations were measured every hour for four hours.

The minimum therapeutic plasma paracetamol concentration for an antipyretic effect is 66 μmol/l.[1] [2] In 18 of our 20 patients the paracetamol concentration never exceeded 25 μmol/l (the lower limit of detection in our assay) and reached only 35 and 29 μmol/l (at two hours) in the remaining two patients. In 10, K-Y Lubricating Jelly (Johnson and Johnson) was used to aid insertion of the suppositories, but this did not effect absorption. There was no fall in rectal temperature over the four hour period.

We analysed the batch of suppositories and found an acceptable 92% bioavailability. As doses of 10 mg/kg have been shown to reduce temperature in preoperative children,[3] we suggest that the poor absorption must be due to patient factors, such as an ileus or interference from anaesthetic drugs. The study by Hopkins *et al* would support this.[1] Although similar doses were used, the plasma paracetamol concentrations were higher (albeit subtherapeutic). As the suppositories were given much later (24 hours after operation), it suggests that the effects of some drug or unknown factor could be wearing off. It would be interesting to re-examine these patients one week later. Whether poor rectal absorption is specific to cardiac surgery and whether other drugs are similarly affected, is uncertain, but needs careful evaluation.

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Archives of Disease in Childhood 1991; **66**: 1005

BOOK REVIEWS

Birth Defects Encyclopedia. Edited by Mary Louise Buyse. (Pp 1892; £150·00 hardback.) Blackwell Scientific Publications, 1990. ISBN 0–86542–088–2.

Any textbook which sets out to comprehensively cover the subject of birth defects is likely to be substantial, and this book is *huge*! The encyclopaedia is produced by the Centre for Birth Defects Information Inc, an independent non-profit making organisation, based in America. The resulting collaboration between international experts is presented in the form of succinct articles, arranged in alphabetical order, on over 2000 birth defects and syndromes.

Do not be put off by the size of this book—if you can pick it up, you will find it hard to put down. It has the same sort of appeal as Smith's *Recognizable Patterns of Human Malformation*, although it is less useful as a diagnostic aid as it contains no feature index. Essentially it serves a different function, providing an invaluable reference source once a diagnosis has been made. The format of the articles is excellent, and the inclusion of over 1700 black and white photographs gives it a satisfying visual content too. Each article title is followed by a list of alternative names by which the defect is also known (for example, for Noonan syndrome these include male Turner syndrome and Ullrich syndrome), as well as a list of conditions excluded by this diagnosis (for example, Klippel-Feil anomaly in the above example). This second list is particularly useful when considering a differential diagnosis. The major diagnostic criteria, clinical findings, and complications then follow. Where this book rises head and shoulders above its competitors is in the subsequent inclusion of details on aetiology, pathogenesis, treatment and prognosis, as well as information on sex ratios, possibilities for carrier detection and prenatal diagnosis, and a brief list of useful references. The address of the American support organisation is, for obvious reasons, less relevant for a British readership. One feature I particularly appreciated was the identification of what are now considered to be pejorative terms (for example, Angelman syndrome is now the preferred term for the condition previously known as 'the happy puppet syndrome'). It is impossible to select particular articles that are worthy of praise, but the sections on chromosomal abnormalities and individual heart defects are very informative and helpful.

The price of £150 may be prohibitive, but is good value, nevertheless. As a result, availability may be limited to that of a reference book in medical libraries, which is a pity. Personally, I think it would be of most value on the shelf of the paediatric office, for those occasions when a child with a rare condition, diagnosed at the regional referral centre, is admitted in the middle of the night with croup, or some such common ailment. How reassuring to be able to familiarise oneself with the essential facts within a minute or two. And just think how good it would look on the consultant ward round the next morning!

SUSAN E HOLDER
Honorary senior registrar in clinical genetics

Comprehensive Epileptology. Edited by Mogens Dam and Lennart Gram. (Pp 843; $180 hardback.) Raven Press, 1991. ISBN 0–88167–646–2.

This book is for the obsessional bibliophile and therefore the specialist rather than the general paediatrician. The authors, both of them well known Danes in the field of epilepsy, have to a large extent achieved the stated aims of the book while leaving one or two important aspects of clinical practice untouched and therefore lacking.

The book has multiple contributors and international viewpoint. With this in mind authors from Asia, Africa, and Latin America present information on local aspects. Whereas this does have the affect of broadening one's psychosociological horizons and entertaining a wider differential diagnosis (for example, of parasites as a cause of epilepsy) there is little value here for the frontline British paediatrician.

Clinical pertinence was also somewhat lacking from other sections. The chapter on the Lennox Gastaut syndrome bore little reference to the educational and behavioural aspects that tend to assume such importance in the life of the families involved. The section on febrile seizures contained none of the recent debate which questions the value of the use of prophylactic anticonvulsant therapy. The sections on neuropsychology and the management of pseudoepileptic seizures are largely theoretical with no helpful considerations of a person's predicament and how it might be resolved.

I enjoyed the section on basic aspects including neurochemistry, neurophysiology, neuropathology, and genetics. The section on classification of epileptic syndromes emphasises the need for the reader to move away from blanket expressions such as, 'grand mal seizures', which are all too often used in clinical parlance without due thought to their meaning.

The chapters on electroencephalography might have considered the use of brain mapping, sphenoidal electrodes, and radiotelemetry and the chapter on neuroradiology for some reason is confined to temporal lobe epilepsy with no consideration of selection for computed tomography. However, the sections on magnetic resonance imaging, emission tomography, and magnetoencephalography all added useful resumes of relatively new techniques.

The medical treatment section offers nearly 200 pages of good reference material on drugs, including the newly arrived vigabatrin and lamotrigine in common clinical usage. The surgical treatment section offers an excellent review of the current state of the art; a reminder to paediatricians to consider surgery where partial seizures are resistant to medication. For some reason the section on organisational aspects considers special centres only whereas this might have been an opportunity to develop other models for community care incorporating medical, educational, and psychosocial aspects.

In these days of quality assurance in the National Health Service, with due emphasis being placed on the information doctors give their patients, I looked eagerly at the section on 'How to live with epilepsy'. This is a good overview but with the emphasis on the adult rather than the child. Doctors will, however, be able to draw good information for their patients from this and the sections dealing with fertility, pregnancy, and the risk of malformation. As we communicate with children and their families the language we use is of great importance. I was pleased the term epileptic as a noun was not present in this book, though I do think, 'children with epilepsy' would have been better than 'epileptic children'. Nowhere, however, was there a section which advised doctors on how they might impart information on the subject to the newly diagnosed and how they might be helped to adapt psychologically. I would conclude by saying this is a book for those with a keen interest and for paediatricians in the frontline other shorter texts such as Niall O'Donahue's *The Childhood Epilepsies* would be better suited to their need.

R W NEWTON
Consultant paediatric neurologist

Child Development: Diagnosis and Assessment. K S Holt. (Pp 202; £15·95 paperback.) Butterworth-Heinemann, 1991. ISBN 0–7506–1035–2.

This comprehensive text provides an account of development as it progresses from the neonatal period to later childhood, including the adolescent age group. The author has drawn together material from various sources that contribute to present knowledge of the basis of development and of methods used in developmental assessment. In addition, there are a helpful set of references available at the end of each chapter. The observations carried out in developmental assessment vary, depending on the age of the child. There are clear descriptions and illustrations of methods used in testing children. In explaining the results attempts are made to draw attention to a wide range of 'normal values' that characterise development. These data are either tabulated or illustrated in a series of diagrams that may be used in clinical practice in assessing the extent of deviant development.

There are three main sections to this book dealing with the basis of development, normal development, and developmental paediatrics. The opening chapter guides the reader through definitions and terminology and leads to other chapters on neural maturation, some theories of child development, and integration of development in the first section of the book. We are then presented with a section on normal development containing a series of chapters on development extending from the neonatal period to the school years. The remaining section on developmental paediatrics has chapters on developmental diagnosis, a developmental approach to handicapped children, and measures of development. These highlight many procedures used as a guide to progress and how to assess the results of tests used by other professionals including psychologists, audiologists, and speech therapists.

The ground covered will be of interest to paediatricians and to doctors in training as undergraduates or postgraduates who wish to increase their understanding of development with a view to including developmental work in their clinical practice.

S W D'SOUZA
Consultant paediatrician

Colour Textbook of Paediatric Dermatology. By William L Weston and Alfred T Lane. (Pp 300; £46 hardback.) Wolfe Publishing, 1991. ISBN 0-8151-9236-3.

The inside cover of this book displays a problem orientated differential diagnosis index enabling the general paediatrician to identify quickly most paediatric dermatological problems. This sets the scene for what proves to be quite a thorough book covering, in 20 chapters, dermatological aspects of paediatric practice, ranging from evaluation of the paediatric patient through to dermatopharmacology. In between there are concise, informative chapters on groups of disorders/ clinical problems presented in an easily digestible but nevertheless comprehensive fashion.

The chapters on papulosquamous disorders and bullous diseases and mucocutaneous syndromes are particularly well written with excellent colour photographs of the various conditions throughout. Each of these chapters is subsectioned in a logical manner with brief outlines of the pathogenesis of the diseases, adding significantly both to the quality of the text as well as the reader's understanding of individual conditions. Also included in each chapter is a reasonable bibliography. On a personal note I would have liked to have seen more emphasis on the embryological development of the skin in the opening chapter. Furthermore, there are inevitable occasions when the requirement for more detail is not met.

In general, however, this book meets all its intended aims, including the specific needs of most clinicians involved in the primary care of children. It would make good reading for paediatricians in training as well as forming a useful part of the premembership reading schedule. The majority of paediatricians, I am sure, would be happy to have this book on their shelves and it would also be useful as a quick reference guide for those with particular interests in paediatric dermatology.

Most paediatric dermatology texts fail to inspire, however the authors in this case have managed to write a most enjoyable book!

PAUL BUSS
Research fellow in medical genetics

Genetic Disorders of the Skin. Edited by Joseph C Alper. (Pp 378; £97 hardback.) Wolfe Publishing, 1991. ISBN 0–8151–0111–2.

This is a good multiauthor book on genetic disorders of the skin that sets out to describe many common and rare conditions which have a genetic basis. The conditions are grouped under useful headings such as hypopigmentation disorders, nail disorders, genetic hair disorders, and biochemical diseases. The presentation, natural history, inheritance, pathological findings, and treatment are given for most disorders described. There is also an attempt to include rare one off case reports, which is helpful to more specialised readers. There are useful tables and figures and it is well referenced. For a reference book it is relatively short and there are omissions. However, the conditions it does describe are covered fully. Some disorders feature in more than one chapter, which is probably necessary for completeness, but there are some discrepancies between the texts reflecting the different authors which is irritating. Dermatologists often use specialised terms to describe syndromes and clinical findings and a glossary would have been useful.

This book seems to be geared to the nongeneticist (which is a shame as geneticists badly need a good reference book on skin disorders). There are three chapters on general genetic principles describing chromosomes and cell division and a very good chapter on genetic counselling. As an introduction to genetics they are very useful chapters, but my worry is that most busy clinicians do not read books from cover to cover but look up a specific disorder. It would have been more helpful to have had a genetic section written by a geneticist for every disease, rather than separate chapters. For example, X linked ichthyosis is described in good detail in the chapter on keratinising disorders but the genetic aspects are covered more fully in the chapter on genetic counselling which is not referenced in the index. In the main dermatological text the gene for X linked ichthyosis is described as being on the short arm of the X chromosome, whereas in the genetic text, it is revealed that the gene has been cloned, as indeed it has!

In addition, clinicians addressing the genetic issue of any disease need to know not only that a condition can be inherited as an autosomal recessive or dominant or X linked recessive, but need an appraisal of which is the most likely mode of inheritance and they want sibling and offspring recurrence risks. This area is not well covered. Many authors are out of date with their description of carrier and prenatal testing and some qualifying statement is needed to urge readers to check on the latest developments.

I think, however, this book covers a wide range of genetic conditions with dermatological features and would be a useful addition to any medical library.

KAREN TEMPLE
Consultant in clinical genetics

Tuberculosis in Children. Edited by Professor Vimlesh Seth. Publication of *Indian Pediatrics.* Official journal of the Indian Academy of Paediatrics, 1991. (Obtainable from: Cambridge Press, Kashmere Gate, Delhi 110006, India.)

Until computerised Medline facilities became readily accessible in our libraries the Indian journals of medicine and paediatrics were largely ignored by western physicians. Even now few British medical libraries stock Indian journals. Consequently a large and fascinating body of literature has remained undiscovered. In many areas of infectious disease the Indian clinical experience is vastly greater than in the west.

Nowhere is this more true than in the field of tuberculosis. In India the annual rate of infection is about 3% and 3·4 million children are estimated to have tuberculosis. Perhaps another 94 million children are at risk of infection. No western books on paediatrics have provided a comprehensive update on the subject of childhood tuberculosis, especially in the context of the developing world.

It is therefore to the credit of *Indian Pediatrics* that they have produced an updated compilation of papers in the form of a book *Tuberculosis in Children* edited by Professor Vimlesh Seth from the Division of Tuberculosis in the Department of Paediatrics at the All India Institute of Medical Sciences. Professor Seth herself has written most of the early chapters on epidemiology, diagnosis, immunopathogenesis, and the immunology of BCG vaccination and the tuberculin test. These chapters are readable, comprehensive, and well referenced. There have been many recent advances in mycobacterial immunology and it is to Professor Seth's credit that she has managed to be so concise. The chapters on imaging in childhood tuberculosis by Doctors S Mukhopadhyay and A K Gupta from the Department of Radiodiagnosis, All India Institute of Medical Sciences present a unique collection of *x* ray films and computed tomograms which are of reasonable quality and reproduction considering the price of publication.

Perhaps the most interesting feature of the book is the chapter on neurotuberculosis by Professor P M Udani, the elder statesman of paediatric tuberculosis in India. He presents a summary of his vast clinical experience in Bombay and highlights the fascinating array of new clinical pictures and syndromes which have emerged over the last decade, largely because of the extensive coverage of children with BCG vaccination and the misuse of powerful antituberculous drugs. Consequently the clinical manifestations of neurotuberculosis have altered.

John Stanford of University College and Middlesex School of Medicine is one of only two non-Indian contributors and elegantly reviews the use of new tuberculins in studying the development of the immune response in children, the assessment of vaccine efficacy, and the value of skin tests in the assessment of immunotherapy.

This is an excellent book and the editorial staff of Indian Pediatrics deserve great credit for its rapid publication. If there is one criticism it is the absence of a review of community based strategies to improve the control of tuberculosis. The book is heavily clinically orientated. Experience of community based programmes to improve case detection, follow up, and monitoring of resistance patterns would have been valuable. At 125 rupees ($15) this is a mandatory buy for any physician contemplating working in a developing country.

ANTHONY COSTELLO
Senior lecturer

Pediatrics—An Approach to Independent Learning. 2nd Ed. Edited by C W Daeschner Jr and C J Richardson. (Pp 548; £22 hardback.) Churchill Livingstone, 1990. ISBN 0–443–08758–X.

Medical students choosing textbooks usually have to decide between a handbook containing brief summaries of common conditions, or a tome with detailed monographs on every rarity. In either case, they may well feel that what they read does not prepare them for their encounter with a patient in hospital or in the community. This book, which was designed as a companion to the clinical paediatric course at the University of Texas at Galveston, offers an original approach to teaching about patients rather than diseases.

The authors' objectives of teaching 'real life' paediatrics is reflected in their arrangement of chapters: forsaking the usual strategy of listing diseases by organ system, they describe a number of common clinical presentations, such as the child with fever, abdominal pain, or enlarged lymph nodes. The main text of each chapter is preceded by a statement of the objectives and a test of prerequisite scientific and clinical knowledge. Much emphasis is placed on assessment of indicators of illness severity. The student will learn how to decide which children may be treated at home, which need further investigation, and which are in 'pre-arrest status'. The text is profusely illustrated with short clinical histories and each chapter is followed by 10 to 20 multiple choice questions, often on patient management problems. One or two sections, such as the chapter on congenital heart disease, revert to a traditional didactic style, but in the main the problem orientated approach is maintained, and there is a consistency of style.

Unfortunately, the same attention to real clinical practice limits this book's usefulness for the British student, who will be unable to learn as independently as the title suggests. He will, for example, need guidance from his tutor on transatlantic differences in immunisation schedules and child protection laws.

It will be difficult to persuade students to buy a book such as this which will not act as a complete reference text. However, I would strongly recommend it for those who teach paediatrics to use as a framework for their own teaching courses.

J DEVLIN
Tutor/senior registrar

Long-term Paediatric Nephrology. By C R J Woodhouse. (Pp 215; £49·50 hardback.) Blackwell Scientific Publications, 1991. ISBN 0-632-02936-6.

In previous decades childhood illness was clearly divided into medical and surgical problems, the former being the responsibility of the paediatricians and the latter that of the surgeon. As the title of the book suggests, there is now a need for regular long term follow up and active medical and surgical management of many childhood nephrological problems through adolescence and into adult life.

Although the book has been written from a surgical perspective, there is a strong emphasis on the importance of good medical care, aspects of growth and development, communication with parents and children, and recognition of the independence of the young adult with chronic disease. In this respect, it emphasises the need for collaboration with colleagues in related specialties, particularly between urologists, paediatricians, nephrologists, transplant surgeons, geneticists, obstetricians, and psychiatrists.

The first four chapters are particularly valuable in setting the scene for a young adult who has emerged from up to 20 years of life with a urological problem, worried over by parents, operated on by surgeons, and coaxed along by paediatricians. The author touches on many aspects of paediatric nephrourological care along with the problems of psychosocial dysfunction consequent on chronic illness in a broad and practical manner, touching on areas rarely covered in standard nephrology or urology texts.

It is clear that for many adolescents and young adults, anxiety about body image and poor self esteem are closely linked to uncertainty about sexual performance and fertility—an area poorly addressed by most paediatricians. Discussion in this area extends to cover the likely outcome of pregnancy and genetic aspects of urological problems, as well as sexual function.

On the surgical side, there is a series of straightforward accounts of procedures with emphasis on newer techniques used now either because of better cosmetic results or to preserve renal function. In addition, there is an extensive review of the literature of long term follow up of important conditions and treatments. The author's personal practice in controversial areas has been stated and while I may not agree with all his views, I enjoyed reading his book. It will make a valuable contribution to the long term management of children and adults with serious urological problems starting in childhood, and will be particularly valuable to adult and paediatric nephrologists and urological surgeons.

K VERRIER JONES
Senior lecturer in paediatric nephrology

Screening for neuroblastoma

Over the last 25 years the overall five year survival for neuroblastoma patients has improved from 25% to 50% or more but in those presenting at over 1 year of age with widespread disease the outlook is still poor with less than 20% five year survival. Could earlier detection by screening improve survival?

An international panel of experts met in Chicago under the auspices of the American Cancer Society in September 1990 to discuss the value of mass screening for the disease and their consensus statement was published in the *Lancet* in February (Murphy *et al, Lancet* 1991; **337:** 344–6).

Work in Japan, Canada, and the UK has shown that screening by testing for high concentrations of catecholamines in urine is feasible. Mass screening at 6 months of age was introduced nationally in Japan in 1985 and by 1988, 337 cases of neuroblastoma had been detected of whom 328 (97%) were alive in 1990. The evidence suggests, however, that many of the tumours detected had an intrinsically favourable prognosis and some, if not many, of them would have regressed spontaneously. Thus national data suggest that screening in Japan has not altered mortality rates there compared with the UK where widespread screening has not been done and there has been no fall in numbers of children in Japan presenting with advanced disease over the age of 1 year. Many of the tumours detected by screening had biological features suggestive of a good prognosis. There was a substantial increase in the recorded incidence of the disease after the introduction of screening indicating that some of the tumours discovered would never have presented clinically.

The Japanese results are clearly very disappointing. It is not known whether screening repeatedly or at a later age would give better results.

The ethical aspects of this screening have not been mentioned by the consensus panel but there are obvious problems. Clearly if screening detects tumours that would regress spontaneously then there is a high price to pay. Parental distress must be incalculable and the children have been treated with surgery and chemotherapy. The *Lancet* report does not give enough data to allow a detailed analysis of the problem. Perhaps studies continuing in North America and the UK to compare screened and unscreened populations will provide such data. From the evidence of this paper the cost-benefit balance at present seems heavily weighted on the side of cost.

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Outcome measurements for child health

The British Paediatric Association (BPA) published last year the report of its Health Services Committee on 'Outcome Measurements for Child Health'. The aim of the report was to recommend a small set of outcome oriented measurements of child health services which health districts (district health authorities) could use to monitor their own performance and to compare themselves with other district health authorities. The committee have confined themselves to drawing up a limited number of measurements which are both practicable and useful as a core for the development of outcome measures in child health.

Two working definitions were used. (1) A health status measurement is a direct measure of some aspect of health in which an improvement is sought, whether or not its relation to any intervention is known. (2) An outcome measurement is a subtype of health status measurement where changes in the measure are known or believed to be directly attributable to a health service intervention.

The committee recommends the following outcome measurements on children resident in a health district:

- Mortality rates in the newborn at 24 hours and 28 days in four birthweight bands from less than 1000 g to over 2500 g.
- The proportion of children aged between 5 and 6 years with congenital deafness whose first hearing aid was fitted later than the age of 15 months.
- The incidence of congenital dislocation of the hip diagnosed after the age of 6 months.
- The frequency of testing for congenital hypothyroidism before the age of 1 week and the proportion of children treated for congenital hypothyroidism who start treatment over the age of 3 months.
- The proportion of children made the subject of an Educational Statement before the age of 6 years in whom the relevant problem was not recognised by a health professional until after the fourth birthday.
- The notification rates for measles and pertussis.
- The proportion of children aged between 2 and 3 in the previous year who were fully immunised against (a) diphtheria, (b) measles, and (c) pertussis by the age of 2 years.
- The proportion of children admitted to hospital with asthma and (a) remain in hospital longer than 72 hours and (b) require both intravenous bronchodilators and intravenous or oral steroids.
- The proportion of children with diabetes mellitus who have concentrations of glycated haemoglobin 50% above the mean normal concentration.
- The number of children under the age of 13 admitted to adult wards as a proportion of all admissions of children of that age.
- The proportion of children admitted for hernia or squint operations who were admitted as day cases.

The committee further recommends that district health authorities monitor the following health status measurements:

(a) Perinatal and infant mortality rates.
(b) Low birthweight rates.
(c) The number of children below the third centile for height on starting school.
(d) Deaths and hospital admissions of children due to road traffic accidents.
(e) The extent of fluoridation.
(f) Smoking in schoolchildren.

The committee finally recommends the establishment of a national confidential inquiry into certain categories of deaths in the age group 12 months to 14 years and a study of bacterial meningitis in children aged between 6 months and 14 years.

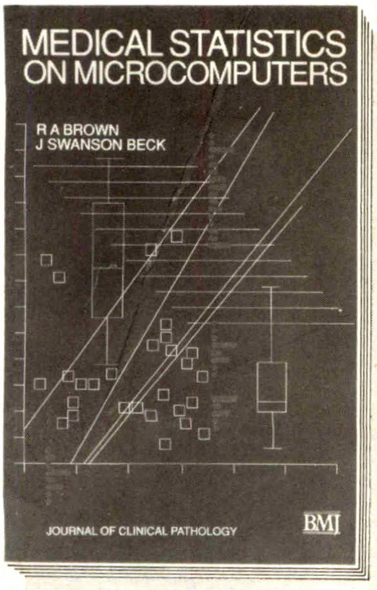
Records in child health surveillance

A joint working party of the Health Visitors Association, the Royal College of General Practitioners, the British Medical Association, and the BPA reported last year on professional and parent held records used in child health surveillance.

The main recommendations of the report were that there should be, as in many other countries, a national Personal Child Health Record showing the child's health and progress in growth and development, which should be held by the parents and made available for professionals to obtain or add information whenever the child is seen. The contents of the record should be in line with the programme recommended by the national Working Party on Child Health Surveillance.

General practitioners and other professionals should hold their own records for their child patients in a similar format and should share the information they hold with the parents. It is essential also for health authorities to keep some key management data on every child to monitor the service and to provide a back up to parent held records.

A D M JACKSON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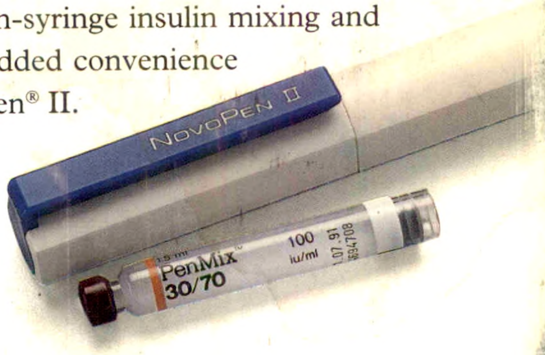

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SEPTEMBER 1992 VOL 67 NO 9

08

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The Journal of the British Paediatric Association

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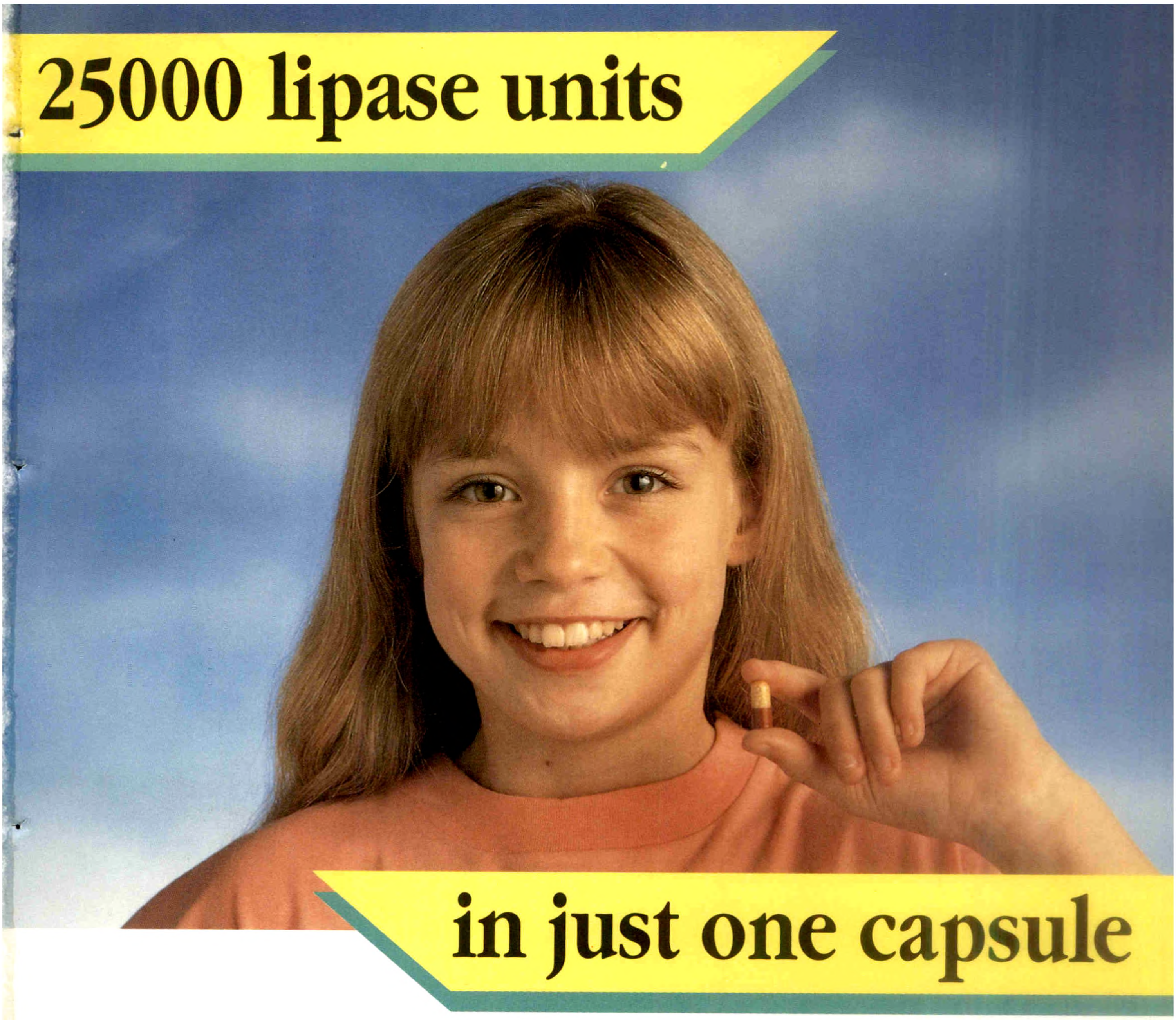

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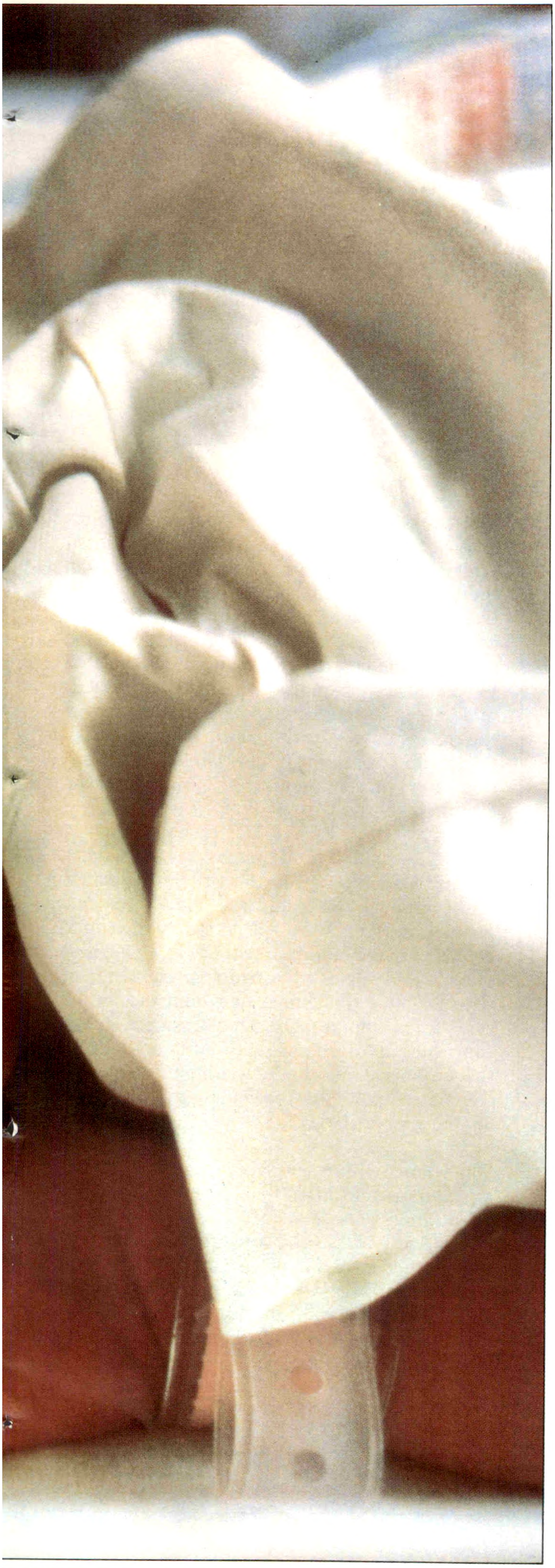

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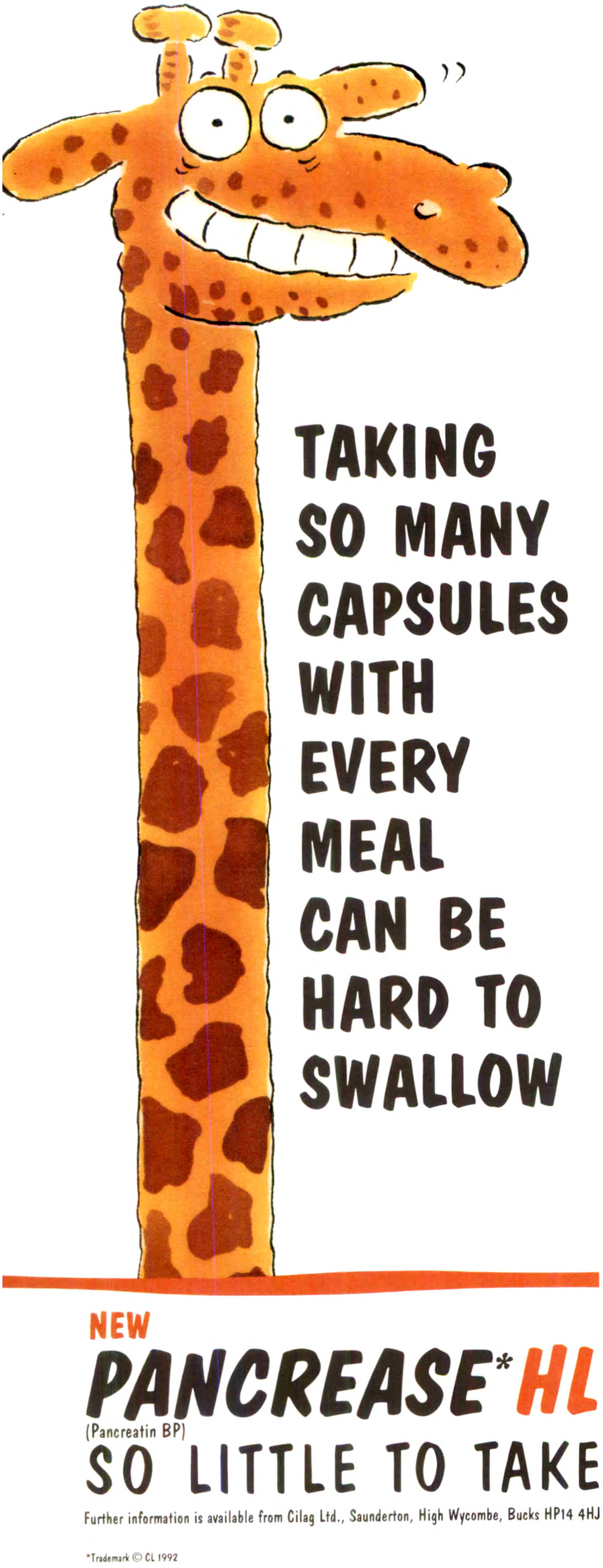
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The winner will receive a cash sum of £200 and an invitation to attend the British Paediatric Association's Annual Meeting, to be held 20–23 April 1993 at the University of Warwick. Subsistence costs for the meeting will be paid by the British Paediatric Association, and travel expenses met from a bequest to the Association by Dr Wilfrid Payne.

ARCHIVES OF
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The Journal of the British Paediatric Association

JAMES SPENCE MEDALLIST 1992

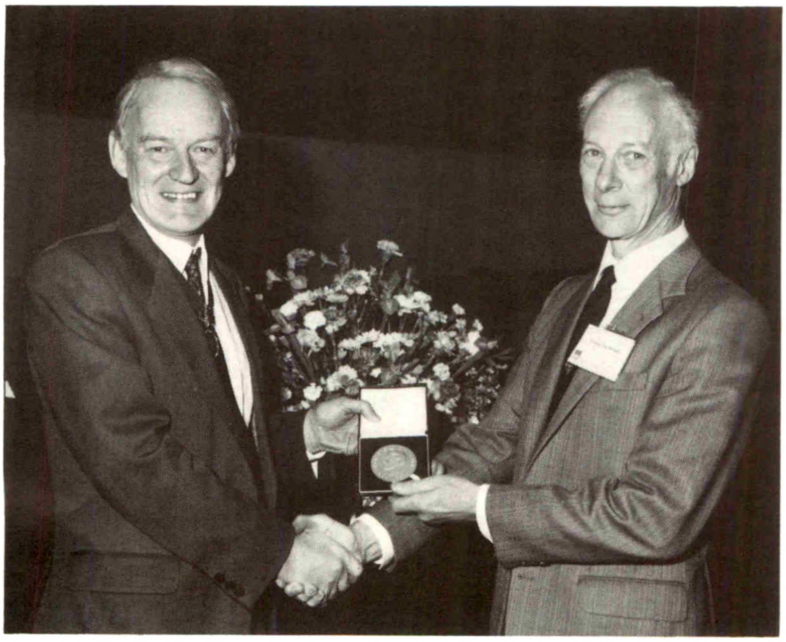
Professor Richard W Smithells

The James Spence Medal was presented to Professor Richard Smithells on the 9 April 1992. Professor David Hull, President of the British Paediatric Association, gave the following citation.

The James Spence Medal is awarded at the recommendation of the Council of the British Paediatric Association for outstanding contributions to the advancement of paediatric knowledge. It is my pleasure this year to present it to Richard Worthington (Dick) Smithells.

Thirty years ago, while a consultant in Liverpool, Professor Smithells wrote four papers which set the scene for much of his subsequent work. They were on neural tube defects, congenital abnormality registers, genetic counselling, and rubella in pregnancy.

By 1962 he had established a congenital abnormality register in Liverpool. To do so required not only a broad knowledge of paediatrics and health sevice practice but also energy, determination, and careful planning. Success depended upon the willing cooperation and good will of many people; the innovator must have been held in high regard. This achievement was all the more remarkable because it preceded the discovery that thalidomide could cause such devastation to the developing fetus. It was this tragedy which was one of the factors which led to the establishment of the Committee on the Safety of Medicines. As a result, drugs are now more thoroughly tested but also, alas, pregnant women and infants are denied potentially beneficial drugs because of the reluctance of the pharmaceutical companies to put their products to the test in these categories of patients. Many of Professor Smithells' early papers were about the effects of drugs especially thalidomide on the developing embryo. His involvement has been both academic and practical: he has served for many years on the Thalidomide Trust.



Professor Hull (left) presenting the medal to Professor Smithells.

Around the same time he was responsible for setting up a genetic counselling service in Liverpool. Common enough now, indeed no good 'Health Trust' should be without one, but in 1962 they were a novelty. True it was a time when the *Lancet* was awash with karyotypes and we were all trying to decide what should be done about them! Then it merely looked complicated, now we know it is.

Already by 1962 Professor Smithells was writing about 'rubella in pregnancy'. This was to remain a continuing interest and a clinical responsibility, for he helped set up the Congenital Rubella Surveillance Programme and was responsible for the Northern Registry.

In 1968 he was appointed Professor of Paediatric and Child Health at the University of Leeds and chose 'Better babies . . .' for the title of his inaugural lecture. The 'dot dot dot dot dots' were included because he had noted that it was the practice for professors to select slightly dotty titles for their inaugural lectures. Having got that out of the way, he then proclaimed his vision. Inaugural lectures are not unlike the 'mission statements' currently so popular with management. He observed that there are three hazards to the life of the newborn baby: being born too soon, being born too dangerously, and being imperfectly formed.

By this time he had already written many papers on neural tube defects, indeed he had shown bravery beyond the call of duty by writing an article on 'anencephaly in Liverpool' while dwelling in that city, thus adding his authority to the mistaken view held by some in the south as to why flat hats are so popular in the north.

The main thrust of his inaugural lecture was that infant mortality was falling and that we should be addressing more vigorously the question of morbidity: making better babies. He observed that 'prevention and diagnosis are moving into the prenatal period', he spoke of collecting fetal cells and making diagnoses, and direct examination of the fetus by photography using ultrasonography but counselled against including these photographs in the family album.

The 1967 Abortion Act allowed early termination of pregnancy if the fetus was a high risk of severe handicap. But he considered that 'the early recognition of congenital defects is a poor substitute for prevention'. So he set himself the task of seeking means of preventing the development of congenital abnormalities. In Leeds he established a laboratory to study the effects of drugs and nutrition on the early development of the embryo and fetus. Results did not come quickly or easily but they came and he and his colleagues established the association between vitamins and neural tube defects. He can take pride in the statistics which are now appearing from round the world showing that the incidence of neural tube defects is falling and that this is a real fall and is not due only 'to seek and destroy' exercises. Some of you will remember the fierce debates about whether the causal relationship between folic acid deficiency and neural tube defects had been established, and whether if it had or not, it was ethical to put it to the test. The pure in science met the pure in mind. Professor Smithells has no fear of the moral argument.

J M Elwood wrote in 1983 that 'if the prevention of neural tube defects by nutritional supplementation is confirmed, it would be one of the great medical advances of the century'. In 1991, the report of the Medical Research Council study concluded that 'Folic acid supplementation starting before pregnancy can now be firmly recommended for all women who have had an affected pregnancy, and public health measures should be taken to ensure that the diet of all women who bear children contains an adequate amount of folic acid'.

In the second half of his inaugural lecture Professor Smithells expressed his wish to see not only better babies born but a better world for them to live in. He was able to make this point powerfully by comparing the size of lettuces grown in different parts of the city of Leeds and the size of adults from different social groups. The lettuces had been grown as an experiment by his grandfather while he was Professor of Organic Chemistry at Leeds University! Professor Smithells emphasised that premature birth and infants of low birth weight are strongly related to social disadvantage and that the problems for these infants do not end at birth. As he put it 'his world is shaky before he can even yell at it'. In his view, the cornerstones of a child's world are first his family and the second his school. So you will not be surprised to learn that Professor Smithells has served on the Executive Committee of the NSPCC, and is an honorary member of its council, he is medical adviser to the Family Fund and a school governor.

Many paediatricians are fine clinicians and energetically promote the health services for children. Quite a few have written successful teaching books, though they are unlikely to be as friendly and useful as Meadow and Smithells. But very few have identified a challenging area for research and pursued it with such determination and success as Professor Smithells.

James Spence Medallists

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Annotations

The radiological dating of injuries

Children who present after accidental trauma virtually always have a clear history of the events associated with the injuries. When there is no history (from an infant or unhelpful parents) or there are other suspicious circumstances one of the many factors involved in the equation that leads to or excludes a diagnosis of child abuse is the dating of those injuries. The injuries may involve the soft tissues, the skeleton, the internal viscera, or the brain. The colour changes exhibited by soft tissue bruises are well known to paediatricians but the dating of injuries to the skeleton, brain and, less commonly the viscera, is a task that usually falls to the radiologist member of the child abuse team. This annotation will centre on the dating of injuries to the skeleton and briefly discuss intracranial injuries.

While there are thousands of published contributions covering the field of fracture repair there is very little on the radiological dating of fractures and even less relating fracture age to child abuse. The most comprehensive review is by O'Connor and Cohen.[1]

Anatomy and physiology of the developing skeleton[2]

At birth the diaphyses or shafts of the tubular bones are composed of fetal or woven bone that lacks haversian systems. However, as periosteal mediated appositional bone formation and remodelling enlarge the overall diameter of the shaft and the width of the cortices, mature bone becomes dominant. This early bone is very vascular and more porous than the maturing bone of older children and adults and better able to tolerate deformation. Pores retard progression of a fracture line but increase the likelihood of compression and it is this reason that makes greenstick and buckle, or torus, fractures more common in childhood. Immature periosteum also differs from that in the adult in being thicker and more loosely attached to the underlying cortex. It minimises displacement of diaphyseal fractures and is capable of faster callus and membranous bone formation.[3] Towards the end of the bone, adjacent to the growth plate is the metaphysis, a site characterised by decreased cortical bone and increased trabecular bone. The trabecular portion undergoes extensive remodelling as the primary spongiosa is transformed into more mature secondary spongiosa. This area of transformation is structurally weak during the period of rapid growth during infancy.[4]

Due to the child's more flexible skeleton and increased amount of stretch allowed by the soft tissues the majority of childhood fractures are undisplaced.

Histological phases of fracture healing

The morphological sequence of fracture repair, namely haematoma, tissue metaplasia, soft callus, hard callus, and remodelled bone dates from the ideas of John Hunter in the 18th century and will be used as the basis for the description here.[5] However, because of the limited number of pathological specimens of paediatric trauma that are available for histological examination and because there are so many variables in the healing process such as the severity of the injury, the degree of displacement at the fracture site and the degree of immobilisation, histologists have relied heavily on animal work. Extrapolation from young animals to young humans may not be valid but it is true to say that the repair process proceeds much more quickly in the infant than the child and both are quicker than the adult. This is especially true of the stage of production of fibrocartilaginous matrix in the callus.[1]

Within hours of a closed shaft fracture of a long bone and the initial haematoma there follows an initial stage of induction, characterised by inflammatory exudate from the ruptured blood vessels of the bone marrow, cortex, periosteum, and surrounding soft tissues. Inflammation is present from a few days to several weeks and is accompanied clinically by soft tissue swelling, pain, and immobility. Osteoclasts are mobilised and become active within four to seven days and with the removal of necrotic bone from the fracture ends the fracture becomes wider and less well defined.

The second stage, or stage of soft callus, overlaps the first and is distinguished by the formation of periosteal new bone and endosteal callus. By the fourth day new osteoid tissue may be seen histologically. Within the next few days periosteal new bone formation is evident and by the end of the first week there is a mass of callus composed of new blood vessels, fibrous tissue, cartilage, and bone. Calcium uptake into the callus begins within a few days of the fracture but does not reach a peak for several weeks.[6] The earliest mineralisation is due to calcification of new cartilage, with new bone formation only evident histologically at one week. It is with the progression of these latter two processes that healing becomes evident radiographically and this stage ends when the bone fragments can no longer be easily moved and the fracture line begins to fade.

At the stage of hard callus the fracture is solidly united and periosteal and endosteal new bone are converted to lamellar bone. The final and longest stage of fracture healing is remodelling with a slow change in the shape of the callus and bone if there is residual deformity. Rotational deformities are very little affected by remodelling. The phenomenon of overgrowth is a feature of fractures of the immature skeleton, particularly femoral fractures. The degree of overgrowth is inversely related to age and in infants it is desirable to allow a degree of overriding at the fracture site to compensate for this complication.

Differences between the abused skeleton and the 'normal' skeleton

In addition to characteristic fractures, for example metaphyseal fractures and multiplicity of sites and differing ages, there are a number of other differences between fractures in the abused child and ordinary 'accidental' fractures that are relevant to fracture healing. Firstly, abuse fractures occur in infancy with very few fractures occurring over the age of 4 years.[7–9] Secondly, there may be delay between the episode of trauma and the time medical attention is sought or given.

This may result in poor immobilisation of the fracture or even refracture through a partially healed injury. A repetitive injury to the same bone within hours of the first injury will produce yet more bleeding but healing will then proceed normally. A repetitive injury a week or more after the initial event will cause disruption of callus as well as further haemorrhage. The latter scenario, in particular, leads to the appearance of 'exuberant callus', a sign observed not only in child abuse but also in other conditions where fractures may present late, for example congenital insensitivity to pain and osteogenesis imperfecta.

Growth plate and metaphyseal fractures

Unlike growth plate fractures in the older child those in the abused child most commonly traverse the most immature primary spongiosa where columns of calcified cartilage are transformed into metaphyseal trabeculae.[10] Metaphyseal fractures frequently do not disrupt the tightly adherent periosteum and will not, therefore, initiate subperiosteal new bone formation. This creates a particular problem when dating of the injury is important. When a periosteal reaction is present it is usually modest in amount and may only produce a haziness of the cortex. When massive periosteal reaction is present it reflects either displacement of the metaphyseal fragment or a shearing injury to the periosteum.[10] During healing, bone resorption will result in indistinctness of the margins of the fracture and endosteal callus will obscure the fracture line and produce a band of sclerosis within the metaphysis but these signs are somewhat subjective. After fracture, discrete radiolucencies extending from the growth plate into the metaphysis have been described and attributed to fracture repair. Trueta and Amato noted an increase in the thickness of the hypertrophic cell zone of the cartilaginous growth plate in rabbits with experimental disruption of metaphyseal vasculature,[11] and Kleinman *et al* have confirmed that these radiolucent extensions of the growth plate into the metaphysis do indeed correlate with cartilage hypertrophy during healing of metaphyseal fractures.[12] They tend to be single and focal with minimal osseous injury and broad and multiple with extensive injury. The depth of penetration of the growth plate into the metaphysis relates to the age of the injury and, although further work needs to be undertaken, it is hoped that by using the known rates of growth of different metaphyses[13] it may be possible in the future to date more accurately a metaphyseal injury from its radiological appearance.

Radiological changes in the soft tissues

Haemorrhage and inflammatory exudate begin immediately after the injury. They obliterate the normal lucent fat planes and well defined muscle boundaries around the injured site and are frequently the first and may be the only evidence of a fracture. In the absence of a major underlying fracture these changes persist for a few days only but more severe injuries may be associated with soft tissue changes which persist for longer.

Response of the periosteum to injury

Periosteal new bone is laid down in response to a number of types of injuries such as infection and thermal injury as well as physical trauma. Elevated periosteum is not visible radiographically until calcium accumulates in the superiosteal haematoma and the new bone. The first appearance of periosteal new bone is dependent on the age of the child, the younger the child the earlier it appears. In the infant it can be seen, radiographically, as early as four days after injury but seven to 14 days is more usual. Cumming, in a study of birth related fractures concluded that the absence of periosteal new bone 11 days after birth should suggest the possibility of abuse.[14] Beyond the neonatal period periosteal reaction delayed longer than 21 days may be a consequence of poor nutrition or vitamin D deficiency. The amount of subperiosteal new bone increases with repeated trauma and continuing subperiosteal haemorrhage, but chronic repetitive trauma may be of such severity as to destroy periosteal new bone as it develops with resultant failure of the usual sequence of changes with healing.[1]

Ultrasonography has been used to demonstrate subperiosteal haemorrhages,[15] occult long bone fractures,[16] and costochondral injuries[17] before radiographs confirm the presence of bony injury and may be a useful supplementary investigation when attempting to date an acute injury. Radionuclide bone scanning with its low radiation dose has gained increasing popularity in recent years but its role is controversial. Sty and Starshak found a false negative rate of 0·8% for scintigraphy which prompted them to conclude that scintigraphy should be the screening procedure of choice.[18] However, Merten *et al* had a false negative rate of 27% for scintigraphy and advised that it should occupy a secondary role only.[19] From the data of these and others[20–22] we can conclude that scintigraphy demonstrates superior sensitivity for rib fractures, especially at the costovertebral junction, undisplaced shaft fractures and subperiosteal haemorrhage. Rosenthal *et al* reported that the earliest fracture demonstrated with radionuclides was seven hours after the injury and that if a bone scan obtained three or more days after injury fails to reveal a focal lesion then a fracture has been exluded.[23] A positive scan steadily becomes less so as the age of a fracture increases but there is no definite time course. The pitfalls of imaging with a bone-seeking isotope are that symmetrical metaphyseal injuries, adjacent to normally 'hot' epiphyseal growth plates, some vertebral body fractures, and many skull fractures may be undetectable.

Fracture line definition

Fresh fractures, including metaphyseal fractures, have sharply defined margins. With the development of an osteoclastic response to necrotic bone the fracture ends become less well defined and the fracture widens. There are no objective criteria to estimate fracture healing using this sign but it is not apparent radiologically before one week and reaches a peak at two to three weeks.

Callus formation

With the production of osteoid and its subsequent calcification and ultimate transformation to bone there is an increase in density along the fracture line. With impacted fractures and other fractures where the periosteum remains intact or little disturbed this may be the only evidence of injury and it is, therefore, a less valuable sign that periosteal new bone and fracture line clarity. Again, movement may inhibit or destroy endosteal callus and a fracture line may remain clearly visible after a bone has united by periosteal new bone. Endosteal soft callus is first visualised as an ill defined increase in density and begins to form soon after the first appearance of periosteal new bone, that is at about 10 to 14 days. When lamellar bone bridges the fracture, about a week later, the stage of hard callus has begun. The chronology of callus formation and fracture consolidation is dependent on age. A birth related fracture may be united at one month but a similar fracture in an 8 year old will be united at eight weeks.[24]

Remodelling

Estimation of the age of a fracture by this criterion is very difficult because initial deformity, the amount of callus produced, and age of the child are major variables. In the young infant with a stable, undisplaced fracture the remodelling process may be complete at three months while the older child with an angular deformity or a markedly displaced fracture may continue to remodel for two years.

Intracranial haemorrhage

Computed tomography is the primary diagnostic method for the evaluation of head trauma and its value in the management of the abused child is well documented.[25–29] The appearance of haematoma on computed tomography changes slowly with time and is well understood.[30] Freshly clotted blood is of higher attenuation (whiter) than brain, becoming the same density as brain from two to four weeks, and less dense than brain after this time, approaching the density of cerebrospinal fluid by six weeks. Chronic subdural haematomas associated with ventricular dilatation may be difficult to distinguish from cerebral atrophy on computed tomography but magnetic resonance imaging (MRI) easily identifies it as chronic haematoma. MRI has been shown to be superior to computed tomography in the investigation of subacute or chronic head injury[31] but the MRI appearances during acute haemorrhage are more complex, change rapidly during the first week, and have a wide differential diagnosis.[32] Nevertheless, once haemorrhage has been identified on computed tomography, MRI can be used to assess its age more accurately if that is appropriate.

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Fungal skin infections

Fungal skin infections or superficial mycoses are common causes of skin disease in most age groups. They include three main diseases—dermatophyte or ringworm infections, candidosis, and pityriasis versicolor. There are significant differences, though in the epidemiology and clinical behaviour of these infections when they present in childhood. This is in part due to variations in rates of exposure in the case of dermatophytosis but in other examples may reflect real differences in the expression of host resistance.

Resistance to skin infection

The factors that determine the outcome of skin infection are divided into innate mechanisms and those that require the expression of immunological memory.[1 2] Innate mechanisms include the capacity for epidermal cells to respond to damage to the stratum corneum by increased proliferation. Although scientific proof is lacking there is no reason to suppose that this capacity varies with age, except perhaps in photoaged skin. Likewise fungal inhibition due to reversible binding by unsaturated transferrin,[3] present in sweat and serum, is not known to be affected by age. However the presence of free fatty acids (FFAs) on the skin surface is known to affect fungi as those of medium chain length inhibit the growth of dermatophytes while facilitating the growth of pityrosporum yeasts. The composition of sebum containing these FFAs changes at puberty when the inhibitory moieties of medium chain length come to dominate. This is believed to be the explanation of the comparative rarity of scalp ringworm, tinea capitis, in postpubertal children whereas pityrosporum infections, such as pityrasis versicolor, are seen more frequently. FFAs appear to act by direct inhibition of fungal growth but they may also interfere with adhesion,[4] the interaction between fungal cell wall receptors with keratinocytes, which is essential for subsequent penetration of the skin.

The other main processes determining the outcome of fungal invasion are antigen reception by Langerhan's cells,[5] the accumulation of effector cells, principally neutrophils, the site of infection via the production of chemotactic factors by the fungi and the activation of T lymphocytes, predominantly helper cells.[6 7] The means by which the latter effect fungal clearance is also not understood. Production of cytokines which amplify neutrophil killing or epidermal growth as well as the activation of keratinocytes themselves to express HLA-DR and elaborate more cytokines such as interleukin-1 are probably equally important. The net effect is that patients with defective T lymphocyte function including AIDS patients are especially susceptible to most superficial mycoses, although unless this is accompanied by appropriate levels of exposure this defect will manifest itself by altered clinical expression of disease rather than by increased incidence. Dermatophytosis in the AIDS patient is an example where bizarre or extensive infections can occur but the diseases are not more common than in the appropriate control groups.[8]

Susceptibility to superficial mycoses may, in some cases, be genetically determined. There is evidence, for instance, for HLA linkage in the candida endocrinopathy syndrome[9] and for an autosomal recessive mediated trait in the tropical infection, tinea imbricata.[10]

Dermatophytosis

The dermatophyte or ringworm fungi are mycelial organisms that produce long chains of cells, hyphae, in order to penetrate the stratum corneum.[11] They do this by the production of proteases which can break down keratin. These fungi cause exogenous infections originating either from other humans or animals or, more rarely, soil. They produce a characteristic group of infections known collectively as tineas whose clinical expression is largely determined by the site of infection, the identity of the organism, and the level of host response.

There are major differences in the epidemiology of infection caused by dermatophytes in children and adults. Foot infection including nail disease (onychomycois) is rare in childhood[12] whereas it is the commonest pattern in adults. The reasons for this are not clear. Childhood nail infections, for instance, are seen occasionally, indicating that the nail is susceptible to attack. One possible reason is the lowered opportunity for exposure to a suitable environment for transmission of infection which is provided ideally by communal changing rooms. Tinea pedis begins to peak in incidence in the teens and early adult life.

The converse is true of tinea capitis, scalp ringworm, which with few exceptions, is a disease of childhood.[13] There are two main sources of infection, animals (zoophilic infections) and other children (anthropophilic infections).[14] With the former the main cause in most countries is the cat or dog ringworm, *Microsporum canis,* although cattle ringworm, *Trichophyton verrucosum* may also occur. Here exposure is sporadic depending on contact with an infected animal. Increased susceptibility in children, as mentioned previously, is the main reason for the development of the infection in childhood compared to adult life. In Europe, the Middle East and some US and Latin American cities *M canis* is now the dominant organism. By contrast ringworm infections caused by anthropophilic fungi are more common in Africa, India, and the USA.[15] [16] While host susceptibility may explain the prevalence of childhood infections to some extent exposure to an infected population is important. Carriage rates of organisms in clinically normal scalps in endemic areas may be as high as 4%.[17] Some of these children may subsequently develop ringworm or the carrier status may be reversed. The combination of high rates of endemicity, mild clinical signs of infection, and inability to mount effective control measures has led to the perpetuation of hyperendemic foci for scalp ringworm. Typical causative organisms are *Trichophyton tonsurans* (USA), *Trichophyton soudanense* and *Microsporum audouini* (Africa), and *Trichophyton violaceum* (North Africa, Middle East, and the Indian subcontinent).

Scalp ringworm is easily treated with griseofulvin; most topical antifungal treatments are ineffective on their own.[18] Newer antifungal drugs such as itraconazole or terbinafine are effective, although their limitations are still not clear. Treatment of *M canis* infections with ketoconazole, however, is often unsuccessful.[19] Griseofulvin is normally given in doses of 10 mg/kg daily for six to eight weeks. Though with zoophilic infections it is not necessary to keep children off school, some measure of caution is advisable with the anthropophilic fungi. Here the traditional method of control is griseofulvin combined with exclusion of infected children from school. There is no study that has examined the combined use of oral antifungals and topical applications such as ketoconazole shampoo as methods of limiting spread. With anthropophilic infections it is comparatively easy to screen for spread within classrooms as even though the organisms of the trichophyton unlike microsporum species do not usually fluoresce under ultraviolet (Wood's) light they can be grown from screening scalp samples. One method is the isolation of fungi from scalp massage brushes passed through children's hair.[20] Our practice is to treat infected individuals with griseofulvin and carriers, that is those with positive culture but no clinical or microscopic evidence of hair shaft invasion, with ketoconazole shampoo.

Cost in developing countries is often a contraindication to effective control. While the cost of griseofulvin is low compared with newer alternatives the price of a six week course for large numbers of children is high where resources are limited. However there is evidence that the use of single doses of up to 1 g of griseofulvin may be effective methods of eradicating infection in the majority of infected children.[13] This method is also highly appropriate as the drug can be administered under supervision by a medial assistant or nurse.

Candidosis

Superficial infections affecting the skin and mucous membranes caused by species of the genus candida are very common in clinical practice. These fungi are normal commensals in healthy hosts, although disease is more likely where there is a defect in individual susceptibility. The carriage rates of candida in normal hosts range from 18% (range 4–66) in the mouth to 12% (range 0–33) in the gastrointestinal tract.[2] In children carriage rates vary considerably. For instance in newborn infants they may reach over 70% in those in neonatal intensive care units.

The commonest superficial infection is oral candidosis, which is seen in infants. Chronic oropharyngeal infection is much less common. Where it occurs it is important to consider the possibility of inherited or acquired immunodeficiency including AIDS and the rare infection chronic mucocutaneous candidosis (see below).

Chronic mucocutaneous candidosis (CMC) is a persistent superficial infection with candida species affecting principally the mouth, the skin, and nails.[21] While originally it was hoped that a deeper understanding of the immunological basis of this syndrome would provide a potential answer to our knowledge of the nature of resistance to infection, the true nature of the immunological defect(s) in this condition is still elusive. It has become apparent though that some of the supposed defects such as reduced delayed type hypersensitivity and neutrophil killing of candida are reversible with successful antifungal treatment. This suggests that some form of immunomodulation by the organism itself may be involved and, for instance, an immunosuppressive effect of circulating cell wall mannan has been proposed as one possible mechanism.[22] The expression of a human iC3b receptor-like epitope by *Candida albicans* is of interest in this context as the presence of antibodies to this substance in the serum of CMC patients has been shown to block iC3b rosetting.[23] It has also been found that patients with CMC are susceptible to other cutaneous infections notably dermatophytosis and human papilloma virus infections and so the defect is not specific to candida.

The classification of CMC has also changed with time. The best known variant is one associated with the polyendocrinopathy syndrome, usually hypoparathyroidism and hypoadrenalism. This is inherited as an autosomal recessive trait.[24] Patients with this form generally have evidence of autoantibodies to other organs and some have involvement of other systems, for example pernicious anaemia or primary ovarian failure. In addition to this type some patients may have underlying hypothyroidism, inherited as an autosomal recessive trait. Other patients have no clear predisposition and are said to have sporadic type CMC. In addition in some families without endocrinopathy there is evidence of either autosomal recessive or autosomal dominant susceptibility.[25] All forms are usually clinically indistinguishable and range from mild to severe, although those with the sporadic form appear more likely to have extensive disease. Rare adult forms of the disease may also occur. It is important to screen children periodically for endocrinopathy because they may develop endocrine disease years after their first presentation with CMC. One further risk factor is the appearance of leukoplakia on the tongue that may progress to squamous carcinoma. However progression appears to be a particular problem in smokers. Other complications include bronchiectasis and potentially fatal bacterial septicaemia.[21]

Treatment of CMC is now easier, although relapse of infection is common. The drug ketoconazole[19] is very effective and itraconazole[26] or fluconazole[27] are alternatives. In each case relapse of oral infection is common and it is important to stop treatment once the mouth is clear, instituting further treatment should this be necessary. The reason for this cautious approach is the risk of drug resistance developing where an azole is used continuously. It is not clear whether this will occur with all azoles but resistant candidosis has been described with both ketoconazole and fluconazole. In future studies it will be important to combine monitoring of changes in the patterns of drug sensitivity with genetic typing (karyotying, restriction fragment length polymorphisms) to check that resistance has truly evolved in the original strains.[28] For severe infections other drugs such as intravenous amphotericin B can be used instead.

Pityrosporum infections

The pityrosporum yeasts are common skin commensals, although their emergence is usually delayed until after puberty.[29] They may cause disease in childhood in two ways. Firstly they have been isolated in large numbers from cradle cap eczema giving rise to the suggestion that they may be responsible for this condition.[30] The situation is analagous to that seen with adult seborrhoeic dermatitis. In addition these fungi have also been found to be a cause of septicaemia in premature neonates; intravenous feeding with intralipid appears to be a risk factor for infection.[31] The route of infection is not clear but is thought to be via an intravenous line. The commonest disease caused by the pityrosporum yeasts, pityriasis versicolor, is rare in childhood.

Conclusions

While superficial mycoses are common in adults, infections in chidren present specific challenges. In the healthy child scalp ringworm remains a problem although in industrialised countries, with the exception of the USA, it tends to be a sporadically occurring disease. In the developing world, however, the prevalence of infection is likely to persist in the face of other more pressing financial priorities. In the immunocompromised patient, including those with HIV infection and CMC, there are still a number of challenges, not only in treatment but also in our knowledge of basic immunopathological mechanisms. The new understanding of the function of epidermis as an immunologically active organ may provide some of the answers that have been so elusive.

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ORIGINAL ARTICLES

Paediatric outpatient utilisation in a district general hospital

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Abstract

Paediatric outpatient utilisation in a district general hospital was studied for 20 general practices that covered a population of 26 433 children. The actions taken by paediatric staff were analysed for 487 new referrals and 2784 review attendances (the latter in 1630 children) over an eight month period.

New referral rates from different general practices varied between 3·7 per thousand children 0 to 15 years and 29·6 with a mean of 13·7, equivalent to 19 per thousand per year. (The national mean based on health district populations is 21·2 per year.) A total of 63% of new referrals and 49% of review patients were aged under 5 years. Over the study period 2·2% of children under 5 years in the population were referred as a new patient, equivalent to 3·1% per year, and 1·3% of children aged 0 to 15 years were referred, equivalent to 1·8% per year. Review attendances on one or more occasion occurred in 6·5% of children under 5 years over the study period, equivalent to 9·2% per year, and for age 0 to 15 years, 4·8% attended once or more times over the study period, equivalent to 6·7% per year. The review attendance rate per thousand child population per practice varied between 59 and 160 with a mean of 81·9. New patients formed 14·8% of the total attendances (the national mean is 18·3%).

Review attendance rates were significantly lower when the general practice was large. Socioeconomic factors suggested by a high proportion of children in the general practice list were associated with a high review attendance rate. Altogether 27·0% of new referrals were seen once only and 32·8% had no tests done. The most common reason for attendance was asthma (11% of new and 19% of review patients). The second commonest was for fits (8·4% of new referrals and 4·7% of review patient attendances).

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There is very little information available upon the utilisation of paediatric outpatient services in the NHS and mostly this is numerical data for health service indicators (HSIs) based on district health authority populations. Information has been published on new referral of children to hospital outpatient clinics for all specialties—rather than just paediatric outpatient clinics—and has been documented at a rate of 100 referrals per thousand children aged 0 to 4 years and 64·3 per thousand children aged 5 to 14 per year.[1] In a review of 1093 children aged 3·5 years forming part of the British births study, 4% had attended a paediatric outpatient clinic one or more times in their lives (excluding neonatal follow up clinic attendance).[2] Variations between districts may partly be related to measures of socioeconomic deprivation.[3] Considerably more information is available upon the use of inpatient hospital services and also of child health clinics.[4–6]

Methods

This study was based on a larger paediatric outpatient audit project. In this project, a form was prepared for each patient by an audit clerk that was completed by the doctor seeing the child. Diagnoses were coded using Read coding and actions taken in the clinic such as further appointment, referral to imaging, pharmacy, pathology, therapists, etc were recorded and analysed in respect of grade of staff and related to the case mix. The details of the referring general practice and the postcode of residence of the patient provided the data reported in this paper.

Over the period of the study between 4 September 1989 and 10 May 1990 (0·71 of a year), 487 new patients were seen and 2784 review attendances occurred in 1630 children.

Review attendances followed a previous outpatient attendance or were for follow up after an inpatient admission, the latter amounting to 9·5% of the review attendances. Excluded from the study were ward attenders and newborn babies reviewed in the maternity hospital.

The majority of the patients, 69%, came from Wakefield and 31% came from the Leeds, Pontefract, Dewsbury, or Barnsley district health authority populations.

Detailed analysis was made of new referral and review attendance from the Wakefield general practices as the population data available showed that these 20 general practices represented 97% of the Wakefield district health authority population (93% for 0 to 15 years) and child population data were available for these practices. The analysis therefore is based on 69% of the outpatient attendances (see tables 1 and 2 and results section (C)).

Results

(A) NEW REFERRALS

Although the majority (87%) of new referrals were from the general practitioner (GP), there were 26, with prior agreement of the GP, from doctors working in the community child health service and a further eight referrals were made

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at the instigation of the community doctors. Thus 7% of all new referrals arose from community child health doctors.

(B) MOST COMMON DIAGNOSES IN NEW REFERRALS

These are given in table 3 and the variable diagnostic coding for similar disorders used in the study are illustrated. There is a need to use groups of Read codes when searching for similar disorders.

(C) REFERRAL PATTERNS FOR GENERAL PRACTICES

The pattern of new referral and review attendances based upon each of the Wakefield district health authority practices is shown in table 4. Detailed analysis was made of new referral rates and review attendance rates per thousand children aged 0 to 15 years according to general practice characteristics: (a) size of general practice child population and (b) the proportion of the general practice list who were in this age band.

(i) GP new referral rates

The number of new outpatient referrals related closely to the size of the practice and the new referral rate per thousand child population 0 to 15 years from each general practice had a mean (SD) of 13·7 (6·5) per thousand over 0·71 of a year (equivalent to 19 per thousand over a year). The referral *rate* of new outpatients per thousand was not significantly related to general practice size or proportion of practice list who were children.

(ii) Review attendances by general practice

Predictably, the greater the size of the practice, the greater the number of review patients seen. The review attendance *rate* per thousand child population aged 0 to 15 years, however, varied between 33·8 and 175 with a mean (SD) of 81·9 (34·2), equivalent to 115·3 per year. The review attendance rate per thousand practice child population was greater when there was a higher than average *proportion* of the total practice list who were children ($r=0{\cdot}6153$, $p=0{\cdot}004$) but the review attendance rate per thousand was smaller the larger the *size* of the general practice population ($r=-0{\cdot}5$, $p=0{\cdot}013$). The observation that larger general practices had lower review attendance rates may imply that bigger general practices are more able to undertake review of complex or serious disorders, perhaps by having a partner with a particular interest in paediatrics. The higher review attendance from the practices with a high proportion of children on their list may be a reflection of socioeconomic disadvantages in the population served.

These observations were also reflected in attendance patterns for asthma, but not for failure to thrive, which may be more closely linked to socioeconomic deprivation.

(D) DIAGNOSTIC CASE MIX

(i) The diagnostic coding made on new referrals

Table 1 Population summary

	Total No	*0 to 15 years*
Wakefield DHA*	145 820	28 520
Wakefield DHA practices†	141 048	26 433
Catchment population:*		
All acute specialties	209 000	
Paediatrics		46 460

Source: *HSIs; †Family Health Services Authority.
DHA=district health authority.

Table 2 Outpatient attendances

	New referrals	*Review attendances*
Total in outpatient study	487	2784
Wakefield DHA practices (%)	336 (69)	1922 (69)

DHA=district health authority.

Table 3 New patient referrals: the most common reasons/diagnoses by Read code groups representing 290 (59·5%) of the total 487 new referrals

Diagnosis	*Read code*	*No (%)*
Asthma/wheezing	H33 R060	57 (11·7)
Fits? (epilepsy in 17)	F25+ R002 and 3	41 (8·4)
Headaches (migraine in 18)	F26 R040	29 (5·9)
Cardiac murmur (significant in four)	G54Z P code R052+	28 (5·7)
Behaviour disorder (excluding enuresis/soiling)	E272 E274 E2C and D ECZ+	19 (3·9)
Urinary tract infection	K190	19 (3·9)
Chronic diarrhoea	A08ZZ R0772 J525	16 (3·3)
Short stature	R0345	16 (3·3)
Abdominal pain	R090+ J521	15 (3·1)
Constipation/soiling	PB2 J520 E277	15 (3·1)
Failure to thrive	R0341 R0342 R0343	13 (2·7)
Recurrent upper respiratory infections	H00 H05Z	12 (2·5)
Vomiting? reflux	J1011 R0701 and 2	10 (2·1)
Other		197 (40·5)
Total		487 (100·1)

Table 4 Outpatients seen related to practice and to practice size aged 0 to 15 years (20 practices)

No (%) in practice population aged 0–15 years	*New referrals*		*Review attendances*	
	No	*No/1000 aged 0–15 years*	*No*	*No/1000 aged 0–15 years*
2419 (20·6)	34	14·1	145	59·9
2414 (21·4)	18	7·5	134	55·5
2150 (18·5)	19	8·8	110	51·2
2038 (17·1)	44	21·6	195	95·7
2030 (18·3)	26	12·8	142	70
1906 (20·2)	23	12·1	117	61·4
1901 (17·5)	19	10	113	59
1526 (16·6)	7	4·5	164	105·1
1478 (19·9)	14	9·5	109	73·7
1439 (17·2)	26	18·1	124	86·2
1298 (22·5)	14	10·8	87	67
1124 (19·3)	10	8·9	38	33·8
1082 (15·9)	32	29·6	105	97
809 (15·8)	3	3·7	46	56·9
753 (18·8)	8	10·6	64	85
570 (22·5)	11	19·3	51	89
509 (15·4)	7	13·7	41	80
430 (21·9)	9	21	69	160
357 (14·9)	8	18·7	33	77·3
200 (49)	4	20	35	175
Total 26 433	336		1922	
Mean 20·2	..	13·7		81·9

Table 5 HSIs 1989 paediatrics group ranking: selected paediatric outpatient indicators

Indictor	*National mean*	*Wakefield value*	*Centile rank*	*In top 20%?*
CL67 (outpatient referral attendances 1000 catchment population)	21·2	28·4	88	Yes
CL65 (outpatient average referral attendances/clinic)	2·02	3·17	94	Yes
CL63 (% of all attendances that are referral attendances)	18·34	22·29	82	Yes
MS21 (consultants/10 000 referrals seen)	32·6	22·7	22	No

Source: Department of Health; HSIs 1989.

and review attendances has allowed further detailed analysis which will be reported separately (R MacFaul, R Long, in preparation). It has also been possible to demonstrate the range of conditions seen by each consultant and by other grades of staff.

(ii) A HSI (CL-63, see table 5) gives the ratio of new outpatients in comparison to the total number seen for each health district, the national mean being 18·34% for paediatrics and for Wakefield is shown as 22·29%. However, for this study the ratio was 14·8% and furthermore, data from this study enables the ratio to be calculated separately for groups of children with differing diagnoses.

Table 6 Frequent review attenders: more than five attendances over the eight month period

Diagnosis	*No of attendances*
Asthma	40
Epilepsy	35
Mental handicap with/without epilepsy or cerebral palsy	31
Arthritis	17
Cystic fibrosis	16
Failure to thrive	16
Idiopathic thrombocytopenic purpura	12
Diabetes	10
Constipation/soiling	9
Brucellosis (one child)	8

Table 7 Action taken by consultant

Consultant	*% New patients seen once only*
A	18
B	36
C	20
Total	28

Table 8 % Follow up or discharge by staff grade

	Further appointment	*Discharge*
Consultant	77·5	20·1
Clinical assistant	83·3	15·5
Experienced senior house officer	84·0	15·1
Senior house officer GPVTS*	81·5	17·5

*General practice vocational trainee.

(iii) The most common reason for attending for review was asthma but the highest review attendance *as a proportion of the total attendance* for any specific condition was for diabetes as there were few new referrals for this disorder. A high proportion of review attendances (compared with new referrals) occurred when the review was for a condition that led the child to attend initially after an inpatient admission—for example, for febrile convulsion, meningitis or acute arthritis, and the child has not been referred as a new outpatient. Other conditions for which there was a high proportion of review attendances in relation to new referrals were mental handicap, cerebral palsy, and epilepsy.

These latter conditions also formed the largest *number* of review attendances, second only to asthma. Reviews after an inpatient admission were expected largely to have been seen by senior house officers, but were also seen by other grades of staff: consultants saw a third of these attendances.

(iv) Frequent review attendances—over the period of the study, 229 attendances were in children attending five times or more. The diagnoses for these children are summarised in table 6.

(E) ACTIONS TAKEN IN CLINIC

Actions taken by the consultant after a child was seen as a new patient were noted: 32·8% had no investigations requested. Altogether 28% out of 487 new patients required no further follow up and the proportion varied between consultants (see table 7); 24% of new patients seen required neither investigation nor follow up.

Follow up appointments are initiated by the paediatric department rather than by the GP and consultants tended to discharge a higher percentage of the patients seen, although the difference between the consultant and the other grades of staff was minimal (see table 8); one explanation for this is that consultants were more likely to see children with chronic disorders who were less likely to be discharged.

(F) PAEDIATRIC OUTPATIENT UTILISATION

(i) Using the Wakefield district health authority general practice population the following figures were calculated: (a) of the new referrals, 63% were under 5 years of age and (b) of the review attendances, 49% were under 5 years of age.

(ii) Over the period of the study (0·71 year) 2·2% of 9070 children under 5 years of age from the Wakefield district health authority practice population of 141 048 children of all ages were referred as new paediatric outpatients (equivalent to 3·1% per year) and 6·5% of all those under 5 years attended once or more as review patients (equivalent to 9·2% per year). For those aged 0 to 15 years these figures would be 1·8% and 6·7% per year respectively (based upon 1268 children who attended 1922 appoint-

Table 9 % Paediatric outpatient utilisation arising from 20 general practices with a child population of 26 433 children

Age	*New referrals*		*Review attendances*	
	Over period of study (0·71 year)	*Per year*	*Over period of study (0·71 year)*	*Per year*
0–5 years	2·2	3·1	6·5	9·2
0–15 years	1·3	1·8	4·8	6·7

ments over 0·71 of a year); see table 9. The HSIs for Wakefield are given in table 5 and allow comparison with the activities of other districts. The new patient referral rate per thousand on HSI-CL 67 appears high and exceptional. However, when analysis is based only on the Wakefield district health authority general practice population, the new referral rate is 13·7 per thousand 0 to 15 years over 0·71 of a year, equivalent to 19 per year and just below the national mean of 21·2. The remaining new referrals appearing on the HSIs are from cross boundary flow from other district health authorities where the population data are less clear. A small number of referrals for paediatric opinions may have been made from Wakefield general practices to other hospitals outside the district. Subsequent estimates, based on the contracting process, suggest that number is small and such referrals would lead to the rates in this report forming an underestimate of the demand for paediatric services.

The observed rate of referral in this study was therefore unlikely to have been unusually excessive and the paediatric outpatient utilisation figures are probably representative of national utilisation. This is the first study in the UK that provides such a population based measure of paediatric outpatient utilisation.

Discussion

This study has analysed GP new referrals and review attendance patterns based upon a known population size, providing some insight into utilisation of paediatric services. Of note is the high attendance of children under the age of 5 years (63% of new attendances and 49% of review attendances) and the proportion seen at least once in a paediatric outpatient department in any given year: 8·5% of children in the age band 0 to 15 years and 12·3% of children under 5 years. These figures are from an extrapolation of the attendance over the 0·71 of a year represented in the Wakefield study period (see table 9). Analysis of monthly attendance shows that there was random variation over the year, more dependent on doctors' leave periods than other factors except for an increase in attendance for asthma in November and December.

Table 10 Paediatric outpatient study: review attendances by diagnosis based on 2784 attendances in 1630 children

Diagnosis	*No of attendances*	*No of children*
Asthma	539	324
Epilepsy	237	120
Fits*	130	99
Failure to thrive	120	79
Cerebral palsy/mental handicap	115	84
Urinary tract infection	99	73
Soiling/wetting	88	49
Headaches	79	54
Cardiac murmur:		
Organic	33	31
Functional	35	33
Short stature	68	53
Recurrent coughs–not asthma	65	58
Constipation	60	38
Arthritis	54	28
Vomiting	42	34
Chronic diarrhoea	33	27
Delayed development	29	20
Child abuse	26	21
Abdominal pain	25	20
Behaviour disorder	13	9
Recurrent infections	12	9
Total (%) of all outpatients	1902 (68)	1263 (77)

*Includes febrile convulsion, apnoea attacks, fits.

Previous studies have examined new referrals to paediatricians as part of analysis of multiple specialty outpatient referrals from the general practice perspective.[7, 8] In East Anglia, an average GP was likely to refer 6·4 children in a year with a 95% confidence interval of 1 to 12, representing 0·5 to 6 referrals per thousand per year with a mean of 3·2. This contrasts with the Wakefield study new referral rate per general practice of between 3·7 and 29·6 (mean 13·7) over 0·71 year, equivalent to a mean annual rate of 19·3 per thousand per year. This large difference may be related to the proximity of the population to hospital services.[4] The Wakefield population is fairly dense urban and semirural in contrast to East Anglia. A large part of the variation in referral rates between individual GPs has not been accounted for and there is a large random effect which is compounded by problems of analysis of small numbers.[4, 8] Average practice list size is felt to be a better denominator for studies and partially compensates for the small number effect.[9] A further study based on an east Birmingham practice of 11 500 people with a new paediatric outpatient referral rate of 4 per thousand children attempted to examine whether the GPs' particular areas of interest may have led to a higher rate of referral and confirmed this to be the case in two of the specialties studied,[10] although not in paediatrics where no partner has a special interest. These studies have been on new referrals and there appear to be no such data reported elsewhere on review attendance rates in paediatric practice related to population size.

There are very few data available on diagnostic case mix for children attending paediatric outpatient departments. An unpublished study reported in 1989 at the British Paediatric Association annual scientific meeting (CMN Bhrolchain, PW Wilkinson), showed that over a four month period in the Wirral, 374 children were referred as new patients, equivalent to a referral rate of 15·5 per thousand per year; 90% were from GPs and 12% from the child health service. Of the patients referred, 30% were discharged after one consultation (28% in the Wakefield study). Asthma was the commonest reason for referral: 12·8% (11·7% in the Wakefield study see table 3) where it was also the commonest reason for attendance as a review patient (see table 10).

This study has shown the scale of paediatric outpatient utilisation in Wakefield. Comparison with HSIs shows that this utilisation was not unusual compared with figures from health authorities in England and Wales. There is a particularly high workload in paediatric outpatients arising from children with asthma. Reduction in hospital attendance may be possible by joint working with GPs especially as a substantial number of the new referrals did not have any test performed. Fewer review attendances for all conditions including asthma, took place from the larger general practices, raising implications for further joint collaboration between consultant paediatricians and GPs.

Consultant paediatricians saw 44% of review attendances in this study and had a tendency to see more chronically ill and disabled children. This study has shown the value of diagnostic information in evaluating the use of resources in outpatient clinics.

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Smart from the start

Babies weren't born yesterday, y'know. Well, let me rephrase that. There is a steadily increasing amount of information showing that quite young babies can take in much more than we used to think they could. There is evidence, for instance, that babies only 2 days old will look at their mother's face in preference to that of a woman unknown to them. A recent article in *Nature* (P E Bryant, 1991;354:19) reviews some new findings by experimental psychologists. Apparently most babies will look at a checkerboard pattern rather than anything else, even a schematic face. They do, however, prefer a face to most other things but their reactions change as they grow older. Babies under 1 month of age will follow a moving face-like pattern in preference to a 'scrambled' face in which the components are in disarray. If, however, the same experiment is done with the realistic and scrambled faces presented to the baby statically then young babies show no preference but by the age of 2 months they do. In a recent experiment M H Johnson and colleagues had an arrangement whereby the babies moved around the patterns. They found that babies up to 1 month preferred to follow a realistic face pattern but older babies had no such preference. P E Bryant suggests that perhaps the older babies just become too smart to continue to be tricked by a pattern which they knew was not a real face. Why very young babies follow a moving face rather than a moving non-face and yet show no preference when the patterns are static is not known. It is suggested that the underlying neurological mechanism involves immaturity of the cortical visual pathways, the preference for a moving face occurring at a time when 'subcortical mechanisms' are important. It is not known, either, whether the preference for moving faces applies to real faces as well as to schematic ones. Whichever way you look at it babies are amazingly perceptive very soon after birth.

ARCHIVIST

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Audit of screening for congenital hypothyroidism

P O D Pharoah, M P Madden

Abstract

The effectiveness and efficiency of the screening programme for congenital hypothyroidism in the Mersey region from 1983 to 1989 was examined by an analysis of laboratory, manual and computerised district records, case notes, and Hospital Activity Analysis data.

Births from 1 January 1983 to 31 December 1989 formed the study cohort and the proportion of live births screened, age when treatment was started, validity of the screening test, and the outcome of treatment were determined. In nine out of 10 districts coverage of the neonatal population by the screening programme was incomplete and there was failure to follow up infants who had not been screened. The sensitivity of the test was 97% and the specificity was 99·9%. In 10% of the positive cases treatment was delayed beyond 21 days, the latest was 26 days.

It is concluded that administrative deficiencies were predominantly responsible for the inefficiencies of the screening programme. The long term follow up of diagnosed cases should become part of the monitoring process.

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Congenital hypothyroidism is one of the main causes of mental impairment in children and is present in about 1:4000 births.[1] Crucial to the management of congenital hypothyroidism is the institution of treatment as soon after birth as possible because the later treatment begins, the greater the degree of irreversible mental impairment.[2 3] This underlines the potential benefits of an early neonatal screening programme. The advent of radioimmunoassay for thyroxine and later of thyroid stimulating hormone (TSH) in small samples of whole blood enabled routine screening to become a reality and programmes were introduced throughout Europe and North America with the aim of preventing mental impairment due to hypothyroidism.

The audit arrangements outlined in the government white paper, *Working for Patients*,[4] have been universally welcomed and, currently, audit is being widely applied in almost all clinical disciplines. The Donnabedian model proposes that an audit may be made of structure, process, or outcome.[5] Structural audit relates to the number and mix of staff and provision of facilities and equipment. Process audit is concerned with what is done by the staff with those facilities and equipment. Ultimately what really matters is outcome audit—that is in measures of mortality, morbidity, and patient satisfaction. It was decided to apply the Donnabedian model of audit to the screening for congenital hypothyroidism. In the Mersey region the screening programme for congenital hypothyroidism commenced in January 1983 and we report here an examination of its efficiency and effectiveness programme up to December 1989.

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Methods

The topic areas for the audit were population coverage, the validity of the screening test, the age at which treatment was started, and the outcome as determined by the level of mental impairment.

COVERAGE

Notification of all births to the district health authority is a statutory requirement. The birth notification register that is compiled from the statutory notifications was used to obtain the denominator population in order to determine coverage.

In those districts that had a child health computer system (CHCS), the birth notification initiated the computerised child health record. The results of the screening test is also entered on to the computer so that the names, addresses, and dates of birth of those children who were not screened could be obtained. The districts may also use a manually recorded system.

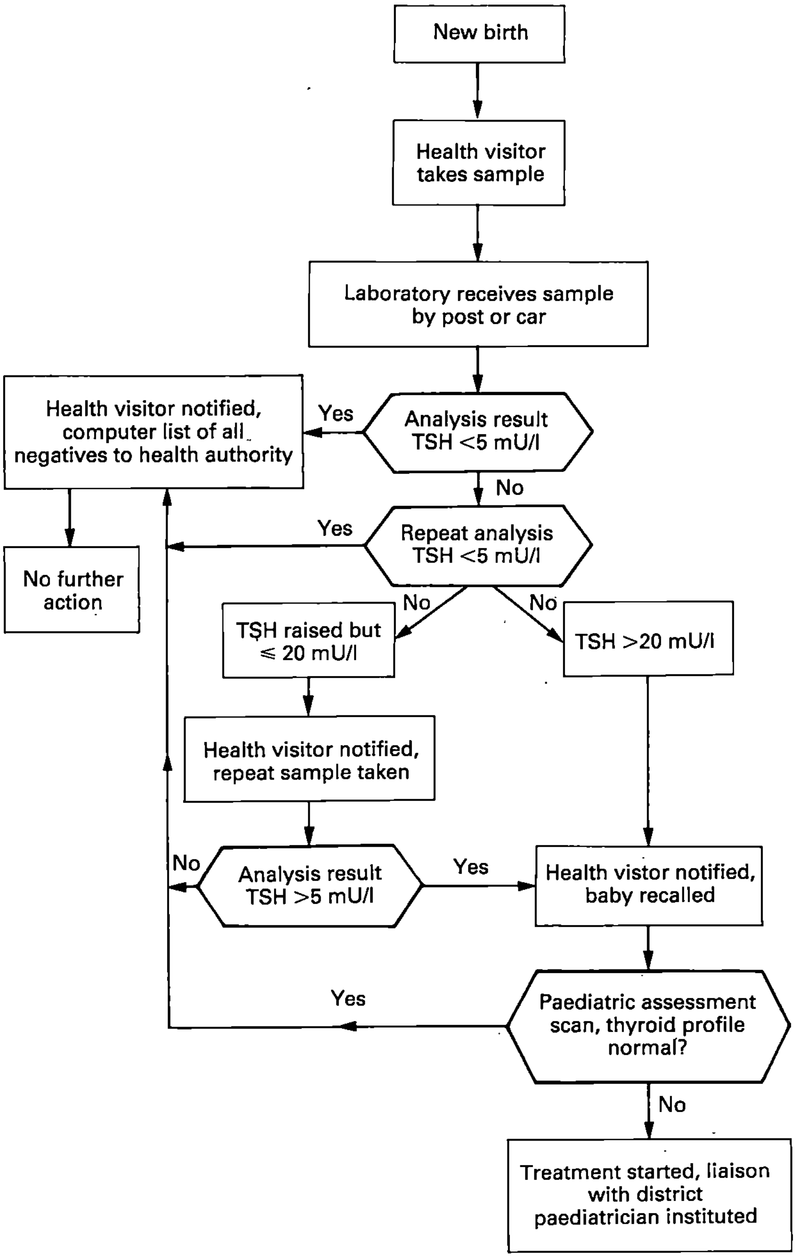
Two problems were encountered when assessing the coverage of the programme. The entry of the child into the birth notification system is determined by the district of residence of the mother when the child is born. The birth, however, may take place in a different district. In these cases, if the midwife omits to enter the district of residence on the card containing the blood spot to be screened, the result will be notified to the wrong district. This may lead to an over enumeration in some districts and an under enumeration in others. The second problem also leads to over enumeration and arises when a repeat specimen has to be taken from the child because the first was technically unsatisfactory.

Two districts had neither a computerised nor a manual system for linking the birth notification with the result of the screening test. Therefore, it is not possible to determine, for these districts, the coverage rate nor is it possible to follow up those children who had been missed in the initial screening process.

Two districts had a manually operated system only. In one of these it was the responsibility of one clerk who ensured that any child with no test result was brought to the attention of the health visitor and followed up. The other obtained a list of names only from the birth notification register against which the test result was entered. As there was neither an address nor date of birth on the list, it was not possible to validate completeness of coverage against the laboratory records.

The remaining six districts all had a computerised child health record system which allowed a validation of the completeness of coverage.

For two years (1988 and 1989) of the study period a validation was carried out. A single regional laboratory performed all the screening tests and for those children who, on the CHCS were recorded as not having been screened, the laboratory records were inspected to confirm the observation. A search of the laboratory records of the adjacent North Western region was also made for those children who were normally residents of the Mersey region but may have been born and screened in the adjacent region. Thus, for the 10 districts in Mersey region, it was possible to determine the proportion of children for whom there was no record of any screening test for congenital hypothyroidism in six districts with a computerised system and in one of the two districts with a manual system.


New birth
Health visitor takes sample
Laboratory receives sample by post or car
Analysis result TSH <5 mU/l
Yes
Health visitor notified, computer list of all negatives to health authority
No further action
No
Repeat analysis TSH <5 mU/l
Yes
No
No
TSH raised but ≤ 20 mU/l
TSH >20 mU/l
Health visitor notified, repeat sample taken
Analysis result TSH >5 mU/l
No
Yes
Health vistor notified, baby recalled
Paediatric assessment scan, thyroid profile normal?
Yes
No
Treatment started, liaison with district paediatrician instituted

Flow chart of screening procedures.

VALIDITY OF THE SCREENING TEST

There are two components to the validity of a test: the sensitivity and the specificity. Sensitivity is determined by the proportion of cases that are correctly identified by the test and is affected by the number of cases that are missed, that is, the false negatives. Specificity is a measure of those without the disease who are correctly identified and is affected by the false positives.

The false negatives were sought using several different sources:

(i) Each consultant paediatrician in the region was asked to identify any child known to them, diagnosed as clinically hypothyroid, who was missed by the screening programme.

(ii) The Hospital Activity Analysis (HAA) information system for both Mersey and North Western regions was scanned for all children admitted with a diagnosis of hypothyroidism and the names checked against the list of those diagnosed by the screening programme.

(iii) In the regional children's hospital the biochemistry department records were checked for any children having thyroid function tests, prescriptions for thyroid hormone replacement therapy were sought from pharmacy records, and the radiology department's records of any child having a thyroid scan were examined.

The false positives were obtained from the regional laboratory and were those children who were recalled for confirmative diagnostic tests after an abnormal screening result but were found not to have the disease.

AGE WHEN TREATMENT WAS STARTED

The aim of the screening programme is to have all blood specimens in the laboratory by the time the baby is 14 days old and to have all positive cases on treatment by 21 days of age.

A flow chart of the procedures from the day of birth to the time that treatment is started is shown in the figure. Reasons for and the length of any delay in instituting treatment were assessed by determining the age of the infant when the blood spot was received by the laboratory for analysis, by the age of the infant when the paediatrician was notified of the test result, and by an examination of the hospital records of all cases diagnosed as having congenital hypothyroidism and noting the age at which treatment was started.

OUTCOME OF TREATMENT

As part of a national study all cases identified by the screening programme are notified to the

Medical Research Council under whose auspices a register is maintained. For each case, a control matched for age, sex, social class, and language background is selected. When aged 5 years the cases and controls are assessed using the Wechsler preschool primary scale of intelligence (WPPSI). However, only 11 case–control pairs within the national data set come from Mersey region and outcome measures based on such small numbers were not considered appropriate.

Results

COVERAGE

In seven out of the 10 districts in the region it was possible to determine the population covered. During the years 1988 and 1989 there were 38 216 births in these districts of whom 37 235 (97·4%) were tested. Within each district the population covered ranged from 96·2–100%. Only one district succeeded in attaining 100% coverage; it used a manually operated system and a clerk had sole responsibility for maintaining it. In only nine cases was the failure of screening attributable to parental refusal. For three districts completeness of coverage could not be ascertained.

VALIDITY OF THE SCREENING TEST

From the screening programme, 60 infants were confirmed as having congenital hypothyroidism. In addition there were two false negatives. One infant, resident within but born outside the region, with multiple congenital anomalies, was admitted because of a severe cardiac anomaly when aged 115 days and found to be hypothyroid. This infant subsequently died. The second case was picked up through the HAA data set as having been admitted for hypothyroidism, although the initial screening result for TSH had been within normal limits. The case records showed that she had been admitted with a hepatic haemangioma at which time a raised TSH but normal thyroxine concentration and bone age were found. A scan showed an enlarged thyroid and treatment was started at 56 days of age.

The sensitivity may be said to be 60/62 (97%), although one of the missed cases was essentially a failure of the screening programme rather than an invalid test. There were 162 false positives who were recalled for retesting as a result of a raised initial TSH. Two of these cases who were recalled for further testing were found to have normal thyroid hormone concentrations despite a persistently raised TSH and were considered clinically euthyroid. The specificity was therefore 193 003/193 165 (99·9%).

*Delay in blood spot reaching the laboratory**

	1983	*1984*	*1985*	*1986*	*1988*
Proportion reaching laboratory after 14 days of age (%)	12·4	11·1	10·2	7·2	9·8
Proportion reaching laboratory after 21 days of age (%)	1·8	1·5	1·4	1·2	2·2

*Records not available for 1987 owing to postal strike affecting receipt of blood spots by the laboratory.

AGE WHEN TREATMENT WAS STARTED

The stated policy aim of the programme is to have all the blood spots for testing in the laboratory by the time the child is 14 days old. The proportion of children for whom this objective was attained and the proportion for whom the delay was over 21 days is shown in the table. There is a trend towards a decrease in the delay over the period of study but much of the improvement was attributable to one district which changed from a postal to a daily van delivery service. In 75% of all infants (whether with a normal or abnormal test result) the test result was available to the consultant paediatrician within 21 days.

Of the 60 cases diagnosed hypothyroid by the screening programme, in 90% treatment was started within 21 days of birth and the latest treatment was started was 26 days after birth.

OUTCOME OF TREATMENT

Because the WPPSI measure was applied to the children when aged 5 years, only those children diagnosed in the earliest period of this study could be included. As there were only 11 such case-control pairs in Mersey region, it was felt inappropriate to present the outcome assessment based on these 11 pairs, but such assessment should await the analysis of the national data set.

Discussion

The 62 cases of congenital hypothyroidism arose from a population of 228 289 livebirths in the Mersey region from 1983–9 giving a birth prevalence of 1:3770. This level of prevalence is similar to the 1:3980 found from 36 centres in 12 European countries and the 1:4200 reported from the USA,[1] which suggests that it is unlikely that a significant number of cases, other than the known false negatives, were missed.

The major failures of the screening programme in the Mersey region are of an administrative nature. Two districts, having neither a computerised nor a manual system of linking the screening result with the birth notification, could not determine what proportion of the newborn population was covered by the screening programme, neither could they organise any follow up of children who had not been tested. Even those districts with a CHCS did not carry out these procedures that ought to be routine in the regular evaluation of any screening programme. Many of the problems of both over and under enumeration due to cross boundary flows of births could be nullified by the simple expedient of requiring that the area of residence of every child is recorded on the card containing the blood spot sent to the laboratory.

The failure to follow up those children who were not tested is also easily remediable and should be made routine. Based on the numbers found in the validation exercise there is likely to be one case missed approximately every five years and this may prove hard to defend if litigation ensues.

The success of the screening programme is ultimately judged by whether or not mental impairment has been prevented in children with congenital hypothyroidism. Follow up studies of hypothyroid infants diagnosed by neonatal screening show normal or near normal intelligence quotients and/or developmental scores when compared with controls.[6 7] However, a note of caution has been sounded: severe fetal hypothyroidism may not be fully compensated by the placental transfer of maternal hormone so that, even at birth, some degree of irreversible mental deficit may be present. This is most likely if there are other stigmata of hypothyroidism, for example delayed bone maturation, present at birth.[8–10] In the national Medical Research Council cohort, infants who were severely hypothyroid at birth, with a plasma thyroxine value of 30 nmol/l or less, had a significantly higher incidence of prolonged jaundice, feeding difficulties, lethargy, umblical hernia, and macroglossia and showed more severe delay of bone maturation on a knee radiograph.[11]

A definitive answer on the outcome of screening for mental impairment must await the results of the national study, nevertheless, regional screening programmes should be monitoring various process measures as part of the audit cycle.

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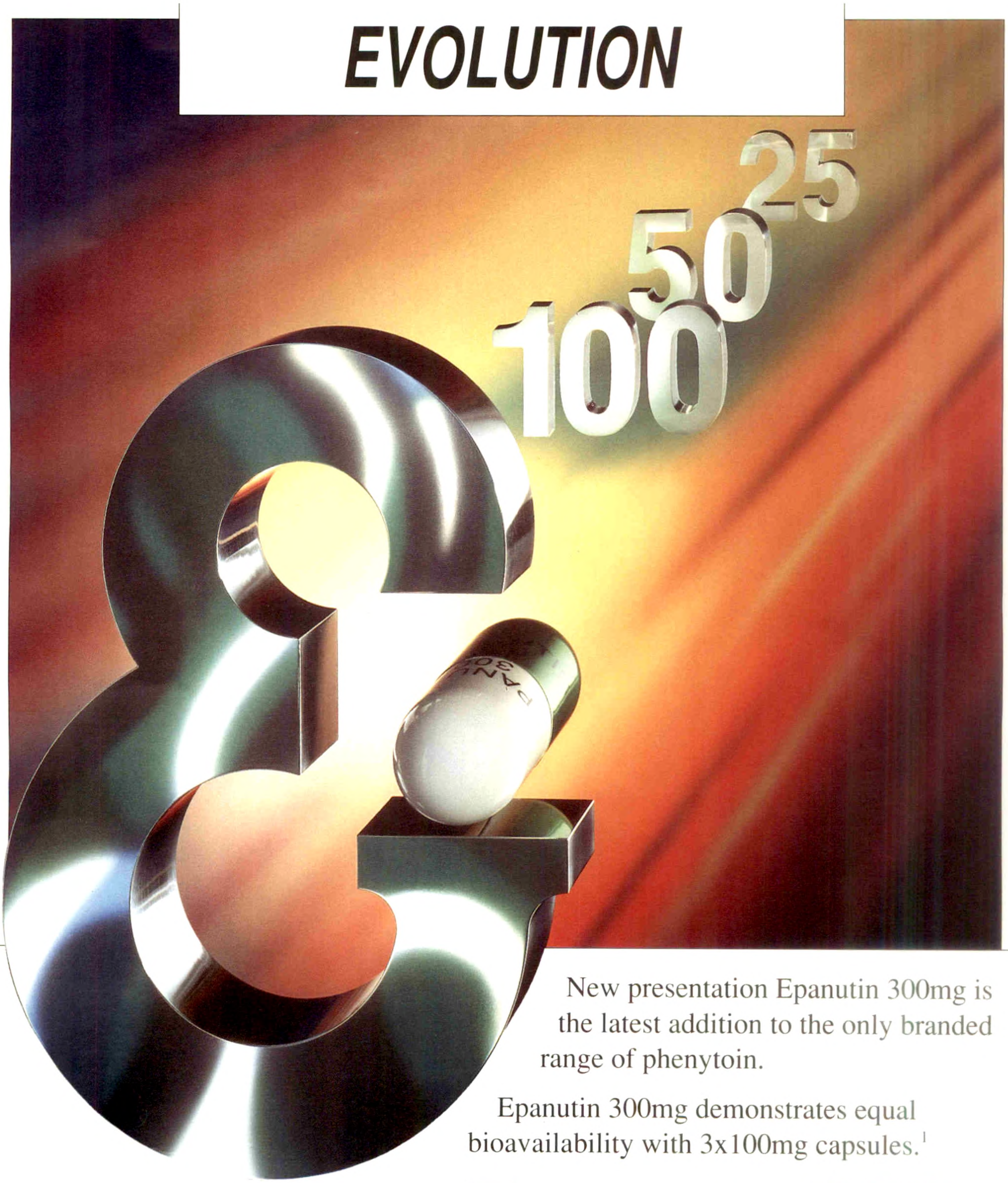

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1. Data on file, Parke-Davis Research Laboratories.

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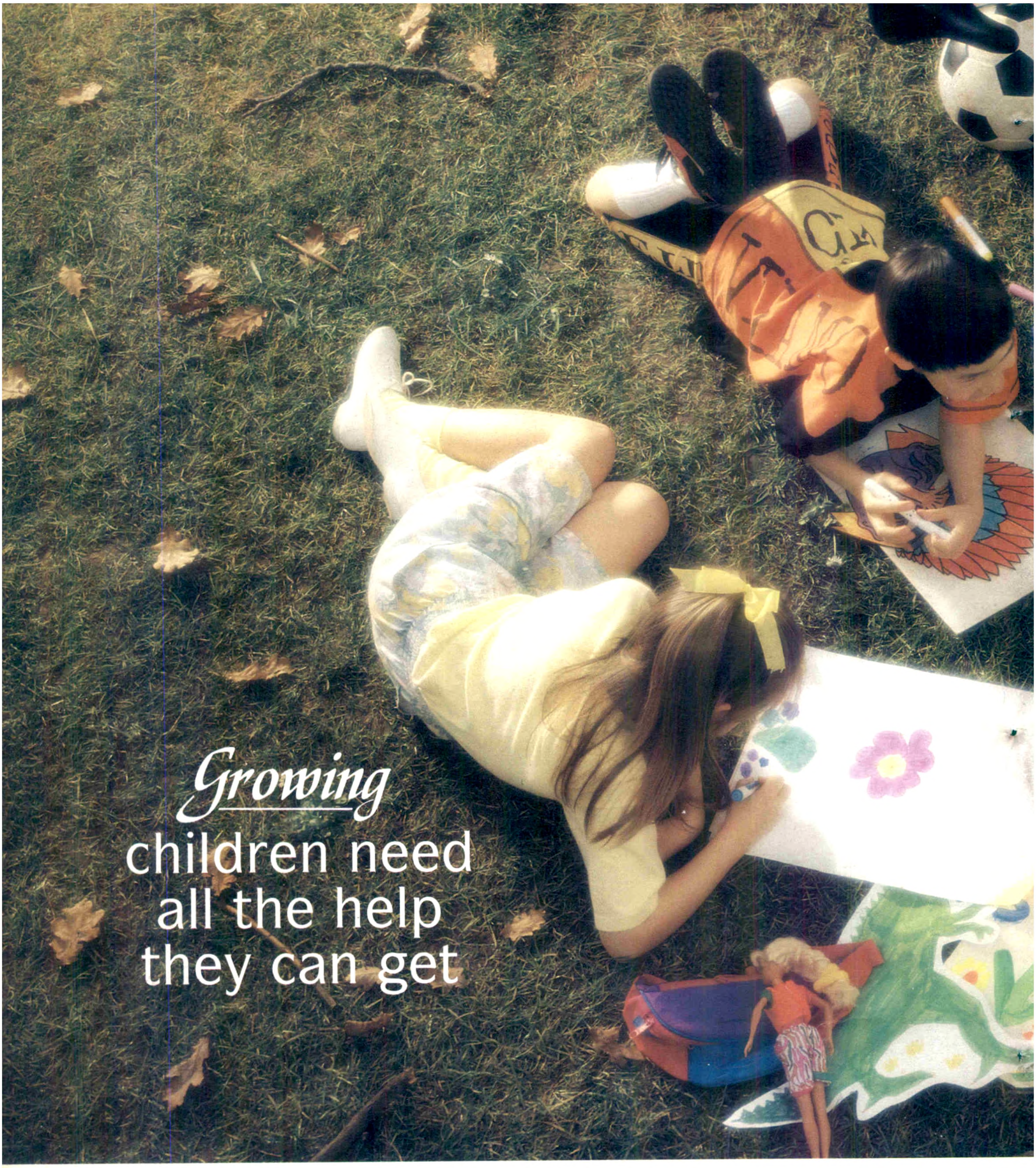

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L-Proline	5.6g
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Recommended dosage for children: The dosage should be increased gradually during the first week of administration to the final dosage ranges indicated below and should be infused over 24 hours:

Weight (kg)	Dosage* (ml per kg bodyweight per 24 hours)
10	24.0
20	18.5
30	16.0
40	14.5

*The duration of infusion should be at least 8 hours.

Caution: The recommended infusion rate should not be exceeded.

Contra-indications, warnings etc: Vaminolact is contra-indicated in patients with irreversible liver damage and in severe uraemia when dialysis facilities are not available. Care must be exercised in the administration of large volume infusion fluids to patients with cardiac insufficiency. Amino acid infusions must also be administered with caution to patients with disturbances in protein metabolism.

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Side-effects: Vaminolact is well tolerated. Rarely, nausea may occur. As with all hypertonic solutions, thrombophlebitis may occur when peripheral veins are used. Abnormal liver function tests have been observed during intravenous nutrition.

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Package quantities: Bottles of 100ml and 500ml.

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Product authorisation numbers: 100ml 187/35/1. 500ml 187/35/2.

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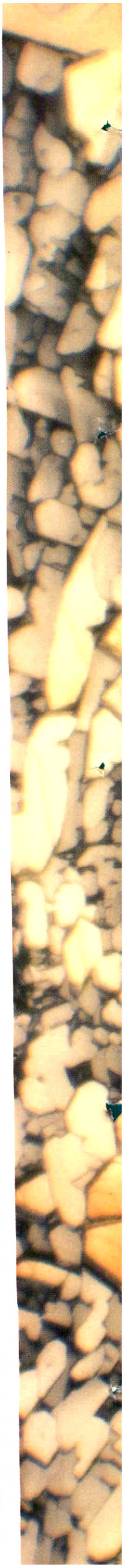

How much nebulised budesonide reaches infants and toddlers?

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Accepted 27 May 1992

Abstract

The amount of budesonide suspension actually delivered to six subjects (aged 4-30 months) by a jet nebuliser and spacer system (System 22) was determined. Two nebulisations were performed in each subject using a filter at the exhalation outlet of the inhalation chamber. An inhalation filter was additionally attached between the facemask and the spacer in the first test. The drug was inhaled during the second test. The nebuliser equipment was washed with ethanol and the amount of drug deposited was determined.

The amount of budesonide deposited in the exhalation filter increased when the inhalation filter was omitted. Only 14% of the nominal dose (500 µg) of budesonide was found in the inhalation filter, increasing from nine to 19% with increasing age. Approximately 75% of the nominal dose was found in the nebuliser equipment.

These findings must be considered when deciding the nominal dose of budesonide suspension to be given to infants and toddlers.

(*Arch Dis Child* 1992;**67**:1077–9)

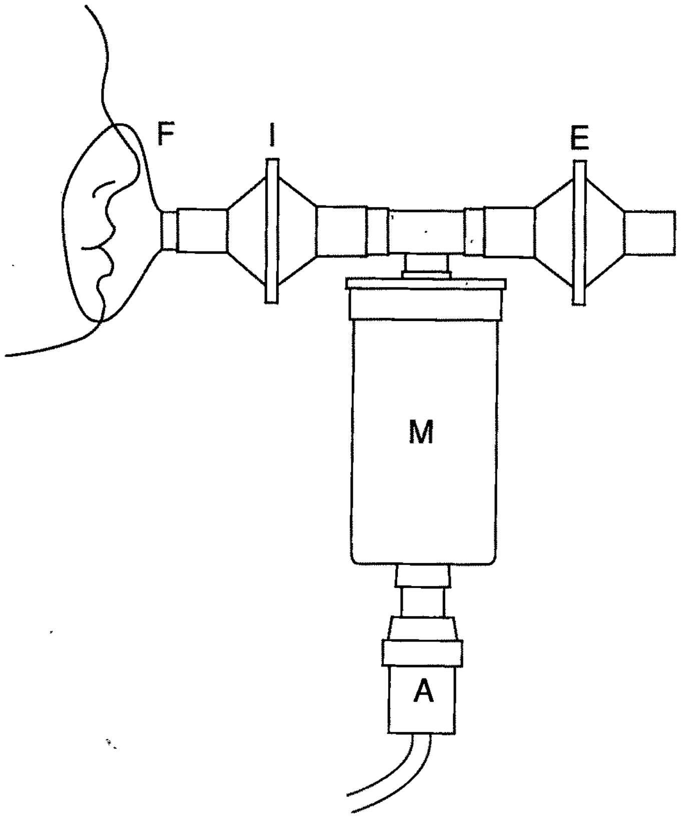

Figure 1 Outline of the inhalation equipment used in test 1. F=facemask, I=inhalation filter, E=exhalation filter, M=Mizer, A=Acorn nebuliser.

Delivery of inhaled drugs to infants and toddlers presents problems as they cannot cooperate sufficiently to use available drug inhalers. Pressurised metered dose inhalers connected to spacers with valve mechanisms and facemasks are prescribed for drug delivery to many infants. This technique, however, is not ideal as the existing valves used in the spacers function poorly at low inspiratory flows. There is also growing concern about the propellants used in the metered dose inhalers. Consequently nebulisers are often used for drug delivery by the inhaled route to infants and toddlers.

Budesonide, an inhaled corticosteroid, is available as a suspension for nebulisation. The dose recommendations are (as for all inhaled corticosteroids) based on information from clinical studies in adults and children in whom lung function can readily be measured. This information is then extrapolated to form guidelines for dose recommendations of the inhaled drug when treating infants and toddlers. Little information is available about doses of inhaled corticosteroids required to treat asthma in early childhood.

As part of a clinical trial we wanted to determine the amount of drug actually reaching the patients when using a neubuliser for drug delivery and following the accepted guidelines for drug dosage.

Subjects and methods

Six male infants and toddlers with a mean age of 15·7 months (range 4–30 months), all with bronchial asthma, were included in the study after informed consent from their mothers. The patients participated in a clinical trial approved by the regional ethics committee in which they received regular treatment with budesonide suspension for nebulisation delivered by the same nebuliser equipment as used in this study.

Jet nebulisation was performed by System 22 (figs 1 and 2); an Acorn nebuliser (Medic-Acid) connected to a Mizer inhalation chamber (Medic-Aid) driven by a CR60 compressor (Medic Aid) at 8 l/min. A facemask (Vital Signs Inc) closely fitted by an air inflatable cuff was connected to the Mizer's drug outlet and held firmly onto the face of the subject.

Two nebulisations were performed on the same day for each patient during an outpatient visit. In the first nebulisation (test 1) two Respirgard-II MQ-303 filters (Marquest Medical Products) were used, one between the facemask and the Mizer's drug outlet (inhalation filter) and the other at the opposite end of the T tube (exhalation filter) (fig 1). In the second nebulisation (test 2) only the exhalation filter was used, thus the patients inhaled the drug (fig 2). The decrease in pressure over the Respirgard-II filter at a flow of 60 l/min is equivalent to approximately 6 mm H_2O. By sucking 25 doses of budesonide (each 0·4 mg) from a Turbuhaler (Astra) through the filter it was found that as little as 0·21% of the total dose passed through the filter (unpublished data). One commercially available respule of 500 µg budesonide suspension (250 µg/ml) was used for each test. The nebulisation time was five minutes for one patient and seven minutes for the other patients.

Each part of the nebulisation equipment was thoroughly washed with spectrometrically pure ethanol and the residual amount of budesonide was determined by reversed phase high performance liquid chromatography at Astra Draco.

Statistical analysis was performed with a personal computer Number Cruncher Statistical System package, and the values are given as means with 95% confidence intervals (CI) in parentheses unless stated otherwise. Correlation analysis was performed by the Spearman rank correlation test. Differences were considered significant under the 5% level.

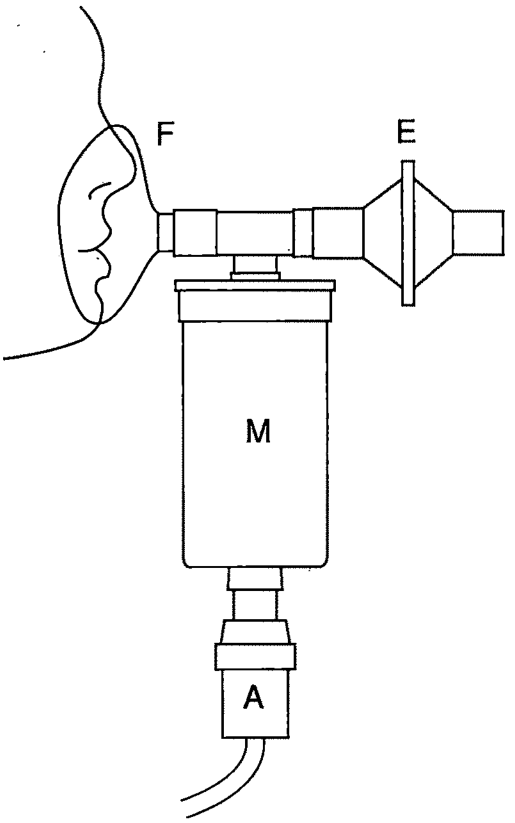

Figure 2 Outline of the inhalation equipment used in test 2. F=facemask, E=exhalation filter, M=Mizer, A=Acorn nebuliser.

Results

The table gives the various amounts of budesonide suspension found in the filters and in the washings of the nebuliser parts. Of the total amount of 500 µg budesonide used in each of the 12 tests a mean of 301 µg (280–321 µg) was deposited in the nebulisers, a mean of 45 µg (32–58 µg) in the Mizers, and a mean of 26 µg (13–38 µg) on the exhalation filters. This gives a total mean of 378 µg which is about 76% of the nominal dose.

A mean of 70 µg (46–95 µg) budesonide was deposited on the inhalation filter (test 1), which is 14% of the nominal dose. No budesonide was found in the facemasks in test 1, but in test 2 a mean of 6 µg (0–15 µg) was found.

The deposition of budesonide on the exhalation filter in test 2 (mean 38 µg; 20 to 56 µg 95% CI) was significantly higher ($p<0·03$) than in test 1 with the inhalation filter present (14 µg, 0 to 28·6 µg 95% CI). Six respules were analysed and had a remaining mean amount of 43 µg (17 to 69 µg) budesonide.

There was no statistically significant difference between the amount of budesonide deposited in the nebuliser equipment in test 1 compared with test 2.

The amount of budesonide deposited on the inhalation filters increased with increasing age (table) from 9% of the nominal dose in the four month old infant to 19% in the 30 month old toddler. The Spearman correlation factor was 0·71, but this was not statistically significant due to the low number of patients.

A mean amount of 32 µg budesonide was not accounted for in test 1.

Discussion

To determine a therapeutic dose of an inhaled corticosteroid for any patient it is essential to know the dose delivered to the patient and the size of the drug droplets. Newman *et al*[1] found that median mass diameter of a budesonide suspension delivered by an Acorn nebuliser and

Amount of budesonide found in various parts of the nebulising equipment for each subject for test 1 (with filter at inhalation) and test 2

Subject No	Age (months)	Test	Budesonide found (µg)					
			Nebuliser	Mizer	Inhalation filter	Exhalation filter	Facemask	Respule
1	4	1	317	44	49	33	—	—
		2	321	41	—	49	0	—
2	13	1	342	26	48	4	—	27
		2	241	18	—	9	2	25
3	4	1	308	41	77	2	—	34
		2	318	31	—	39	1	21
4	15	1	291	30	56	6	—	73
		2	249	51	—	45	5	76
5	30	1	283	60	107	31	—	—
		2	308	99	—	57	18	—
6	28	1	341	43	85	7	—	—
		2	287	55	—	30	8	—

CR60 compressor was 5·2 μm. The droplet size of the nebulised suspension is therefore within the optimum respirable range. In a second study Newman *et al*[2] showed that the output of budesonide suspension with the Acorn nebuliser and the CR60 compressor was 35% of the nominal dose when using a volume fill of 2 ml. Clinically, however, information about the amount of drug actively inhaled is equally important as the detailed knowledge of output by a nebuliser system. Our results show that less than 20% of the nominal dose reached the patient.

The reason for this discrepancy is difficult to explain. We chose a nebuliser equipped with a spacer to avoid spilling of the drug into the environment by a continuously working nebuliser. This would otherwise have occurred as the minute volume of infants and toddlers is smaller than the aerosol output by the nebuliser and compressor system at 8 l/min. Even the nebuliser and spacer system seems to be of limited benefit in terms of drug delivery to the patient, however, as local deposition in the spacer occurs when the nebuliser's output exceeds that of the minute volume of the patient. The deposition in the Mizer was, however, small compared with the almost 75% of the nominal dose found in the nebuliser, the latter finding agreeing with previously reported results.[2]

As steroids are soluble in lipids (in contrast to the commonly used β_2-agonists and sodium cromoglycate), any water based drug delivery must be in the form of a suspension. This increases the viscosity of the suspension, slowing down the nebulisation time even though the aqueous part of the suspension is readily nebulised. The nebulising time did not influence our results, however, which may be explained by the findings of Newman *et al* that the optimum nebulisation time for a budesonide suspension is five to six minutes.[2] Other studies with water soluble substances have shown similar results, such as that of O'Callaghan *et al* who suggested that the optimum nebulisation time for sodium cromoglycate was five minutes, by which time 80% of the total drug output was nebulised.[3]

The amount of drug not accounted for in test 1 (mean 32 μg) may have escaped through the air entrainment hole on top of the spacer or remained in the respule.

The exact amount of drug deposited and its distribution within the lungs in our patients is not known. Silverman has argued that drug delivery by jet nebulisers to a freely breathing young infant is negligible.[4] Watterberg *et al*, however, stressed that giving drugs by this route, albeit with a small yield, was not futile.[5]

The variation (approximately 10%) of dosage deposited in the nebuliser equipment was not greater than would be expected from commercially available systems. The finding that as little as 15–20% of the nominal dose was available under optimum conditions for inhalation by these patients is worrying, however.

Unfortunately there are limited ways of delivering inhalation steroids to toddlers and infants, though various spacer devices attached to metered dose inhalers do exist. As there is increasing concern about the propellant gases in the metered dose inhalers, nebuliser solutions or suspensions of drugs are becoming more important as a means of drug administration. Furthermore, Zainudin *et al*, measuring the deposition of bronchodilators in the lungs of adults, found a significantly higher peripheral deposition of drugs using a nebulised solution rather than dry powder or metered dose inhaler.[6] They also showed that gastrointestinal deposition was significantly lower with the nebulised solution compared with the metered dose inhalers, though the total amount of drug delivered by these two systems did not differ significantly. These results obtained in adults may not be directly transferable to children. It may be assumed, however, that the amount of respirable particles reaching the lungs rather than the gastrointestinal tract in infants is higher with nebulised rather than pressurised aerosol drug delivery.

An unexpected finding in our study was the discrepancy of drug deposition on the exhalation filters with an inhalation filter present or absent. This phenomenon was seen in all our subjects and a rationale for this is lacking. As the resistance in this hydrophobic filter is low it is unlikely that this influenced the results. It may be speculated that some of the drug 'stuck' to the inhalation filter which, when this was omitted, would be exhaled and deposited on the exhalation filter. This raises the question that our estimates of available drug to the subjects might even be too optimistic!

When treating infants with inhaled corticosteroids it is imperative to keep the potential systemic side effects to a minimum. Thus even if the amount of drug delivered to the infant is similar using a metered dose inhaler with a spacer attached or a nebuliser, it seems advantageous to use a nebuliser for this type of drug. However, with as much as 80% loss of active drug with the current nebuliser systems, the costs of treatment could potentially be greatly reduced if more efficient delivery systems were available. The important conclusion to draw is that the huge loss of active drug to the delivery system must be considered when treatment dosage is determined for the individual patient. Furthermore it is important to establish which factors determine the drug delivery for inhalation with respect to the age and tidal volume of the patient.

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Archives of Disease in Childhood 1992; 67: 1080–1081

What do parents know about vitamins?

M L B Ko, N Ramsell, J A Wilson

Abstract

Parents of 120 children attending child health clinics answered a questionnaire on their understanding of vitamins. Fifty four children (45%) were taking vitamins; 12 (22%) were given the wrong dose. Only 19 parents (35%) knew when to stop supplements and 25 (46%) did not realise overdosage was potentially harmful. Only six children (11%) were receiving professional supervision. This indicates a need to improve parental understanding and professional supervision.

(*Arch Dis Child* 1992;67:1080–1)

Vitamin supplementation to children has been a longstanding practice. In particular, since the reported increased incidence of rickets in Asian children in the late 1970s, people are more aware of the need of supplementation.[1] The Department of Health and Social Security stated in 1988 that 'at present it remains prudent to safeguard infants by giving supplementary vitamins' and recommended that 'vitamins should be given to infants and children from age 6 months up to at least 2 years and preferably 5 years.' Parents are able to obtain their supply of vitamins from child health clinics under the Welfare Food Scheme.[2] However, there are also many alternative preparations available to parents from other sources, including chemists and health food shops, without a prescription. Therefore it is difficult to supervise the administration of vitamins to children by their parents.

Little is known about the general public's understanding of the use and purpose of vitamins. The majority probably do not treat them as a form of medication and are unaware of the potential harm of inappropriate administration.[3] Prompted by a recent case of gross hypercalcaemia due to chronic vitamin D overdosage in which the parents had not obtained their vitamins via a medical source and had not received supervision,[4] we carried out this study to find out parental understanding of vitamin supplementation and the degree of supervision received among our local population.

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Subjects and methods

Parents of 120 children aged between 6 weeks and 5 years, who attended five of our local child health clinics, were interviewed by two doctors using a structured questionnaire. The parents were chosen at random and the distribution of their ethnic origins (59% white, 32% Asian, 6% Afro-Caribbean, 3% others) suggests that they were a fair representation of the local population (UK and Irish 70·2%, New Commonwealth and Pakistan 24·1%, and rest of the world 5·7%; Census 1981, Harrow area statistics). They were asked questions to determine:

(a) If their children were given vitamins,

(b) If vitamins were given appropriately according to the DHSS guidelines,[2]

(c) If they understood the use and purpose of vitamins,

(d) If they were aware of the potential dangers of overdosage, and

(e) If they had been receiving professional advice and supervision.

The questionnaire was designed so as to minimise subjective evaluation.

Results

Tables 1 and 2 show the results obtained. There were 54 children on vitamins (45%); 15 of these children were already on fortified infant formula milk which contains adequate amounts of vitamin supplements and therefore some may feel they were on vitamins unnecessarily. Their parents were advised to stop supplements until they were weaned on to cows' milk. There were 15 children aged under 2 years who did not receive any form of supplementation and some of them were advised to start supplements according to the DHSS guidelines.[2] Of the 54 children on vitamins, 16 parents obtained their vitamins privately (30%), 34 were advised to start on vitamins by a health professional (63%), usually the health visitor (33 out of 34). Only six continued to receive professional supervision

Table 1 Number of children on vitamins and their age distribution

Age	*No of children*	*No on vitamins*	*No not given vitamins*
Birth–4 months	35	12	23
4 months–1 year	37	16	21
1–2 years	22	16	6
2–5 years	26	10	16
Total	120	54	66
Children on both fortified milk and vitamins		15 (13%)	
Children under 2 years who received no vitamin supplements from any source		15 (13%)	

Table 2 Information from the parents of children receiving vitamins (n=54); results are number (%)

Able to name vitamin preparation correctly	24 (44)
Able to define correct dosage to be given	42 (78)
Aware of when to cease supplementation	19 (35)
Advised to commence vitamins by professionals	34 (63)
Currently receiving advice from professionals	6 (11)
Vitamins obtained from sources other than child health clinics	16 (30)
Unaware of dangers of overdosage	25 (46)

(11%) and only 19 knew when to cease supplementation (35%).

Twelve children were given the wrong dose (22%), but fortunately all had been given a smaller dose than recommended. Parents of 25 children who were on vitamins did not realise that overdosage was potentially dangerous (46%), and all of their children were receiving preparations that contain vitamins A and D, where harmful overdosage has been well documented.

Discussion

The results of this study show that a large number of parents do not have sufficient knowledge of vitamins to be able to administer supplementation to their children correctly and safely. The population studied is biased towards parents who may be better informed than the general public, as they attend child health clinics and therefore have many contacts with health professionals. The majority of parents interviewed received professional advice, usually from the health visitor, before their children started on vitamin supplements; thereafter, most of them stopped seeking professional advice but continued with the supplements. This may partly be due to decreased contacts with health visitors with the increasing age of their children. This may also explain why so few of them have any ideas how long to continue supplements. Some parents do not realise that they can obtain vitamins relatively cheaply from child health clinics and pay more for similar preparations elsewhere. The most disturbing result is that almost half of the parents were not aware of the dangerous overdosage.

It also appears that health professionals are not very effective in advising parents about vitamins. General practitioners, health visitors, clinical medical officers, and other paediatricians should use their parental contacts, especially during child health surveillance, as opportunities to discuss the use of vitamins. Establishing a unified local policy on feeding and vitamin supplementation would be helpful for professionals and would avoid confusion and contradictory advice. Written or printed advice would help to reinforce the points discussed. There is very useful information on dosage and recommended duration of vitamin supplementation and also warning of overdosage in the booklet *Birth to Five Years* published by the Health Education Authority, which is available to all first time mothers.[5] It is also useful to point out that the information in the national model of parent held child health records seems inadequate as it merely states 'ask your health visitor about the need for extra vitamins and fluoride' (Castlemead Publications, 1990).

The results of this study suggest that more effort should be made to educate the general public on the use of vitamin supplementation. With the recent surge of interest in supplementing children to improve their cognitive functions,[6] it is especially important to make the public aware of potentially harmful effects of inappropriate administration of vitamins. Health professionals should also aim, and be reminded, to improve supervision.

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Archives of Disease in Childhood 1992; **67**: 1082–1085

Effect of taurine supplementation on fat and energy absorption in cystic fibrosis

M De Curtis, F Santamaria, P Ercolini, L Vittoria, G De Ritis, V Garofalo, F Ciccimarra

Abstract

In 10 children with cystic fibrosis and persisting steatorrhoea, supplementation with taurine (30–40 mg/kg/day) was given for two months as an adjunct to the usual pancreatic enzyme treatment. A three day fat and energy balance was performed in patients with cystic fibrosis, before and after the supplementation, and in seven healthy controls who did not receive taurine.

Faecal fat was measured by a gravimetric method and stool energy was determined using a bomb calorimeter. Patients with cystic fibrosis, before and after taurine, and healthy controls received the same fat and energy intake (calculated by a dietitian). In patients with cystic fibrosis taurine did not produce any improvement of steatorrhoea (mean (SD) faecal fat 8·7 (3·3) *v* 11·2 (7·0) g/day, respectively before and after the supplementation), of faecal energy loss (0·978 (0·468) *v* 1·133 (0·539) MJ/day), of faecal fat expressed as percent of fat intake (13·4 (5·6) *v* 15·1 (9·8)%), and of faecal energy expressed as percent of energy intake (9·9 (3·6) *v* 11·2 (5·7)%). Healthy controls had significant lower fat (3·5 (2·3) g/day) and energy 0·576 (0·355) MJ/day faecal losses.

In conclusion, taurine failed to decrease significantly fat and energy losses. Our study does not support the use of taurine supplementation in the nutritional management of cystic fibrosis.

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The best known gastrointestinal complication of cystic fibrosis is pancreatic deficiency, which is present in 85% to 95% of patients.[1] When untreated, pancreatic insufficiency may be responsible for a high degree of morbidity and may affect growth and nutrition. Adequate pancreatic enzyme replacement is required in order to correct nutrient malabsorption, but fat absorption often remains suboptimal despite the use of pancreatic extracts and of drugs which affect duodenal acidity.

As the predominance of glycine bile acid conjugates with almost complete disappearance of tauroconjugates could play a part in the fat malabsorption in cystic fibrosis,[2] taurine supplementation has been proposed as an adjunct to standard treatment. Nevertheless, the results of published papers are conflicting. A significant improvement of fat absorption after taurine supplementation was demonstrated by two different groups,[3–5] whereas the studies of Thompson *et al* concluded that taurine is not indicated in the nutritional management of cystic fibrosis.[6 7] In addition to this, Fitzpatrick *et al* were unable to demonstrate a change in fat solubilisation in patients with cystic fibrosis with ileal resection after taurine supplementation.[8]

To determine whether taurine could play a part in fat malabsorption in cystic fibrosis, we studied the effect of taurine on fat and energy malabsorption in a group of patients with cystic fibrosis with various degrees of intestinal malabsorption that were only in part corrected by pancreatic extracts.

Patients and methods

PATIENTS

Ten patients with cystic fibrosis, seven boys and three girls, with a mean age of 7·7 years (range 2–13 years) were admitted to the study. The inclusion criteria were the persisting clinical symptoms due to an inadequate correction of the pancreatic insufficiency despite the enzyme replacement (mainly, persisting steatorrhoea and failure to gain weight while on an unrestricted diet). The patients had a Shwachman clinical score ranging between 45 and 96 (mean 71) and a degree of respiratory involvement judged from mild to severe. No ileal resection had previously been performed. No patient had clinical and biochemical signs of liver and biliary tract diseases and no one had a weight: height ratio <5th centile. Vitamin supplementation, aerosol treatment, and physiotherapy were unchanged during the study.

All patients were supplemented with an enteric coated enzyme preparation of pancreatin (Pancrease, Cilag). The number of capsules, ranging from a minimum of six to a maximum of 20 a day in the whole study group, remained the same during the study.

DESIGN OF THE STUDY

The experiment was performed on an ambulatory basis and the patients, who were well at the time of the study, remained clinically stable for the whole period of supplementation. Taurine (O-Due, Nativelle) was administered for two months twice daily at a dose of 30–40 mg/kg/day as suggested by Darling *et al*.[4]

Before and two months after starting the supplementation a fat and energy balance study was performed in each patient. Weighed food intake was recorded for a period of six days by a daily diary and a dietitian controlled the records to check for errors. The weighed food intake was analysed using food composition data.[9]

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Gross energy intakes were estimated by multiplying the intakes of fat (39·3 kJ/g), protein (as nitrogen×6·25; 23·6 kJ/g), and carbohydrate (17·6 kJ/g) by their respective heat of combustion values.[10] All stools, collected in the final three days of the record period, were kept in polyethylene bags and immediately frozen. Coal tablets were used as charcoal markers between the start and the end of the collection period.

All the patients were cooperative and no gross errors were found in the daily diary or the procedure for stool collection. During the collection periods the fat content of the diet was not different from the patients' usual diet (about 3 g/kg/day).

A fat and energy balance study was also performed in seven healthy children, with a mean age of 10 years (range 6–12 years), who had no known gastrointestinal and metabolic diseases. They were studied as controls and did not receive taurine supplementation.

ANALYSIS

The pooled three day stools were weighed and dried in an oven at 99°C for 24 hours. The weight of the dried stool was recorded and expressed as a % of wet stool.

Fat analyses were performed on the dried stool samples. A modification of the gravimetric method of Zuckerman *et al* was used.[11] Four weighed samples of dried stools (0·5–2 g) were subjected to acid hydrolysis by boiling in 4M hydrochloric acid. The hydrolysate was filtered and the filter papers were washed with hot water until neutral pH was achieved. They were then dried and extracted with petroleum ether (60–80°C) into preweighed aluminium cups. The extraction was performed in a Soxtec Ht 1043 extraction unit (Tecator). The cups containing the extracted fat were dried and weighed again, and the difference in cup weight was defined as the sample's fat content.

Energy was determined on dried stools using a ballistic bomb calorimeter (Gallenkamp) as reported elsewhere.[12]

Results are given as faecal fat (g/day), faecal energy (MJ/day), and % of fat intake and % of gross energy intake. All the values are expressed as mean (1SD).

The significance of the difference between two arithmetic means was evaluated with the paired and unpaired Student's *t* test and differences between means were considered significant where $p<0·05$.

Results

Taurine supplementation was well tolerated and no side effects were noted. All patients complied with the treatment, as written records of the daily consumption of taurine and of pancreatic extracts were reported by the parents.

In patients with cystic fibrosis daily fat intake was not different in the two periods of stool collection (before taurine, 70·5 (22·5) g/day; after taurine, 76·3 (21·3) g/day). In healthy controls, fat intake was 79·4 (27·8) g/day.

In patients with cystic fibrosis the weight of wet stools was not different before and after taurine supplementation (179 (116) *v* 168 (61) g/day). The dry weight expressed as a % of wet weight in both groups was 24·1 (4·4) *v* 25·8 (5·6)%, respectively. In healthy controls the weight of wet stools was 141 (101) g/day and the dry weight 20·5 (5·1)% of faecal wet weight.

Data about faecal fat losses in patients with cystic fibrosis show that taurine administration did not improve faecal fat loss (before taurine, 8·7 (3·3) g/day; after taurine, 11·2 (7·0) g/day; $p<0·006$). Values of faecal fat loss in healthy controls were significantly lower than those found in patients with cystic fibrosis before taurine (3·5 (2·3) g/day *v* 8·7 (3·3) g/day; $p<0·001$; fig 1).

As shown in fig 2, in patients with cystic

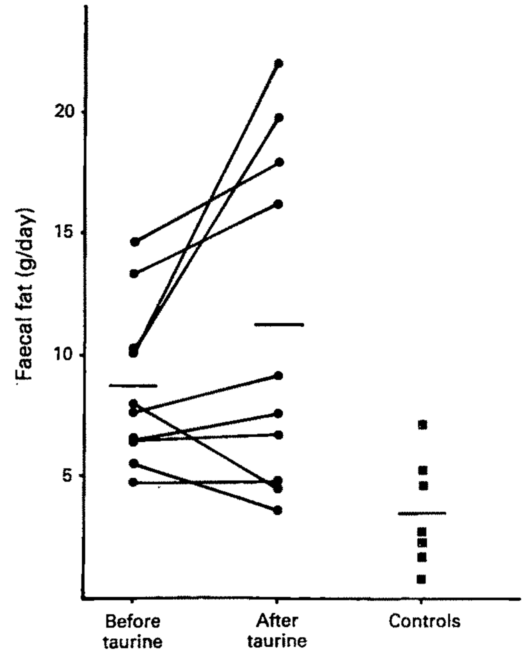

Figure 1 Daily stool fat expressed as g/day in cystic fibrosis patients before and after taurine supplementation and in the control subjects. The bars represent the mean values.

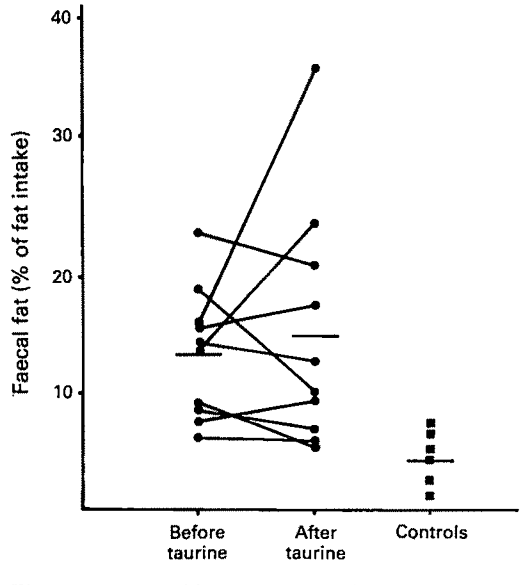

Figure 2 Daily stool fat expressed as % of fat intake in cystic fibrosis patients before and after taurine supplementation and in the control subjects. The bars represent the mean values.

fibrosis the faecal fat expressed as % of fat intake was 13·4 (5·6)% before taurine and 15·1 (9·8)% after taurine (the difference was not significant). In controls the faecal fat expressed as % of fat intake was lower than in patients with cystic fibrosis (4·3 (2·2)%; $p<0·001$).

Gross energy intake was 10·111 (2·691) MJ/day and 10·442 (2·575) MJ/day in patients with cystic fibrosis, respectively before and after taurine; in controls subjects it was 10·065 (2·215) MJ/day.

In patients with cystic fibrosis, faecal energy loss was not different in the two periods (before taurine, 0·978 (0·468) MJ/day; after taurine, 1·133 (0·539) MJ/day). Healthy controls had a mean faecal energy loss significantly lower than patients with cystic fibrosis (0·576 (0·355) MJ/day *v* 0·978 (0·468) MJ/day; $p=0·037$; fig 3).

As illustrated in fig 4, in patients with cystic fibrosis faecal energy expressed as % of gross energy intake did not change before and after taurine administration (respectively, 9·9 (3·6)% *v* 11·2 (5·7)%; the difference was not significant). Healthy controls had a faecal energy expressed as % of gross energy intake significantly lower than patients with cystic fibrosis (5·5 (3·0); $p=0·009$).

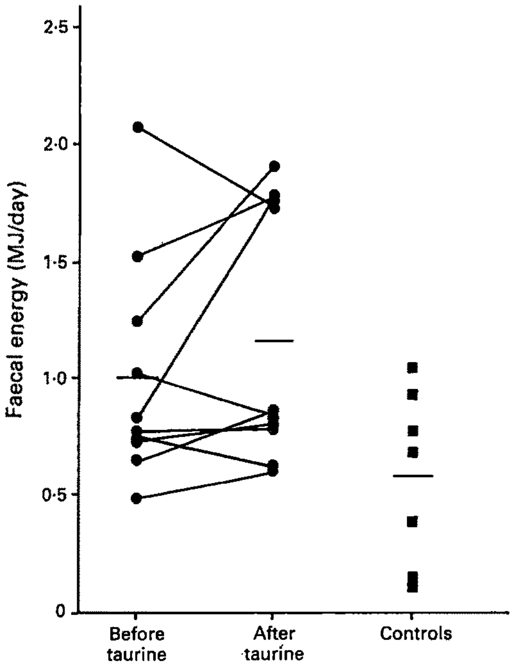

Figure 3 Daily stool energy losses expressed as MJ/day in cystic fibrosis patients before and after taurine supplementation and in the control subjects. The bars represent the mean values.

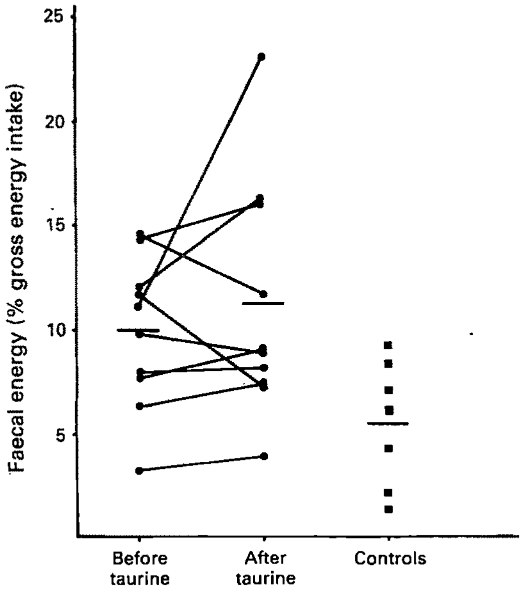

Figure 4 Daily stool energy losses expressed as a % of the gross energy intake in cystic fibrosis patients before and after taurine supplementation and in the control subjects. The bars represent the mean values.

Discussion

To our knowledge this represents the first longitudinal study that measures both faecal lipid and energy losses in patients with cystic fibrosis before and after taurine supplementation. The main consequence of pancreatic insufficiency in cystic fibrosis is the failure to digest and absorb some components of the diet. Fat and nitrogen malabsorption are common in these patients and the faecal energy losses reflect the nutrients' malabsorption.

As enzyme replacement diminishes but does not normalise the amount of fat and nitrogen lost in stools, the use of other drugs that can improve fat malabsorption has been suggested in cystic fibrosis.[13] Nevertheless, a definitive resolution of the symptoms due to steatorrhoea is rarely achieved. In this study we were unable to demonstrate that taurine leads to an improvement in the absorption of fat and energy in 10 children with cystic fibrosis who had persisting fat malabsorption despite appropriate enzyme treatment. These findings contrast with most of the reports about the use of taurine in cystic fibrosis,[3–5] but are similar to the conclusions of other studies, which did not support the therapeutic use of taurine in the nutritional management of cystic fibrosis.[6 7]

The disagreement in the results of the studies on taurine supplementation in cystic fibrosis could be related to differences in the characteristics of the study population. People who suggest the use of taurine in cystic fibrosis recommend it particularly in patients with a significant degree of steatorrhoea, but our results, like those by Thompson *et al*,[6 7] do not reveal any improvement in fat and energy absorption, even in cases with a low baseline high fat and energy losses.

The dose of taurine and the length of the supplementation cannot represent a bias: in our study taurine was given at the same dose and for the same period as in another study that concluded that taurine was effective in cystic fibrosis.[5] However, Thompson *et al* showed that the glycine:taurine conjugates ratio is remarkably sensitive to even relatively small doses of taurine.[7]

Recently, another group has published data regarding the energy and fat content of stools in patients with cystic fibrosis.[14] Similar values of both faecal fat and faecal energy have been found in our patients.

In healthy patients we found a slightly higher fat and energy faecal excretion than those reported by Murphy *et al* (respectively 3·5 *v* 2·2 g/day and 0·577 *v* 0·339 MJ/day).[14] Our values are similar to those seen in adults.[15]

Faecal energy does not represent only malabsorbed energy: in addition to maldigested and unabsorbed dietary residues, faecal energy losses can be due in part to colonic bacteria and to products from cellular lysis, which represents up to 30% of the faecal energy.[14]

In our study, fat absorption was estimated in terms of steatorrhoea and of the percentage of dietary fat intake, which had been strictly checked by a dietitian. In the previous studies no detailed data about the dietary intake of fats are given: the variation of fat intake itself may account for changes in faecal fat loss unrelated to fat absorption. Furthermore, in one of these studies the authors give results in terms of 'steatorrhoea', that is quite different from the percent of fat intake.[4]

In cystic fibrosis some evidence exists for impairment of fat absorption, which is distinct from the maldigestion of fat consequent on absence of pancreatic lipase. Some steatorrhoea may persist with enteric coated enzyme preparations, even when optimal intraluminal pH for exogenous lipase is achieved by the use of cimetidine and sodium bicarbonate.[13] A reduction in the bile acids pool resulting from decreased ileal reabsorption may be a partial explanation.[2]

The efficacy of taurine in cystic fibrosis is based on the assumption that this amino acid provides the necessary substrate for the synthesis of taurine-conjugated bile acids, which in turn, could improve the micellar solubilisation of lypolitic products.[16] Our patients had no liver and biliary tract disease. Nevertheless, as ileal mucosal bile acids malabsorption has been postulated in cystic fibrosis,[17] we cannot definitely state that our patients did not benefit from taurine supplementation because taurine-conjugated bile acids are less efficiently absorbed across the ileum.

In our study a variability in the response to supplementation appears in some individual patients. An explanation for this and for the considerable variability of the response to taurine supplementation among the various groups[3–7] is the great heterogeneity of fat malabsorption in cystic fibrosis, which can be due both to lipase deficiency and to decreased solubility of bile acids micelles in the unstirred water layer. In this view the hypothesis of the association between taurine deficiency and biliary abnormalities in some patients with cystic fibrosis appears interesting. This finding supports the conclusion that taurine could be helpful only in selected patients, particularly if fat malabsorption is more related to the bile acid component than to the exocrine pancreatic insufficiency itself.

Taurine supplementation is also a controversial issue in low birthweight infants, who usually present with a low fat absorption.[18] The reasons for fat malabsorption in these babies are various and not fully defined: pancreatic lipase may be reduced, bile acid pool sizes, rate of synthesis and intraluminal concentrations are low, and absorption of bile salts may be impaired. No agreement has been reached about the effectiveness of supplementation of formulas with taurine on fat absorption in low birthweight infants.[18–20]

In conclusion, pending further studies on taurine administration in cystic fibrosis, we do not recommend an indiscriminate supplementation with taurine in every patient with cystic fibrosis suffering from persisting steatorrhoea. More work is still necessary to confirm the exact role of taurine in cystic fibrosis.

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The value of serum IgG titres against *Pseudomonas aeruginosa* in the management of early pseudomonal infection in cystic fibrosis

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Abstract

We report the results of a clinical trial. Patients enrolled had serum IgG titres against *Pseudomonas aeruginosa* above the control range. Assignment to the observation or treatment group was by minimisation. Significant signs or symptoms in any patient prompted antipseudomonal treatment. In addition, the treatment group received antipseudomonal treatment at intervals of four months until the serum IgG titre returned to the control range. *P aeruginosa* was isolated intermittently from patients in the main trial. Nineteen patients were enrolled (12 observation, seven treatment). After one year in the trial changes in parameters studied, including forced expiratory volume in one second, IgG titre, serum IgG concentrations, and frequency of *P aeruginosa* isolation had improved in the treated group and worsened in the observation group.

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Pulmonary infection with *Pseudomonas aeruginosa* is an important cause of morbidity and mortality in patients with cystic fibrosis.[1] Once the organism has become established in the lungs it is never completely eradicated, even after aggressive antimicrobial treatment, hence the early stages of infection of the airways and lungs are important.

In the past, there were two major problems associated with assessing the presence and severity of the early stages of infection: first, the significance of a few intermittent isolations of *P aeruginosa* was unclear. Secondly, there were no consistent changes in any clinical or immunological parameter until infection became chronic and ineradicable, so it was not always clear whether treatment was necessary and, if given, whether it had been beneficial.

Measurement by enzyme linked immunoadsorbent (ELISA) of serum IgG antibodies specific for *P aeruginosa* seemed to overcome these problems. In chronically infected patients the IgG titre correlated significantly with clinical measures of the severity of infection and the response to treatment.[2] Furthermore, an increase in titre, to above the control range, preceded isolation of the organisms in the majority of patients.[3 4] It is possible that antibiotic treatment given to patients in the early stages of pseudomonal infection, indicated only by a rise in antibody titres to above control values, may be effective in eradicating *P aeruginosa*, and preventing or delaying the onset of pseudomonal infection.

This study was designed to determine the effect of antipseudomonal treatment on patients with raised serum IgG titres and intermittent isolations of the organism.

Patients and methods

PATIENTS

All patients attended the paediatric and adult cystic fibrosis clinics at our hospital. The criteria for entry were patients who had *P aeruginosa* isolated from respiratory cultures and who had a modest increase in serum IgG titre (270–2000). Patients with chronic symptomatic chest infection associated with high titres (>2000) and patients on corticosteroid treatment or nebulised antipseudomonal antibiotic treatment were excluded from entry.

Patients were assigned to a treatment or observation arm in each trial. Allocation was done by minimisation[5] after stratification for age (0–10 years, 11–20 years, >20 years), sex (male, female), Shwachman score (<70, 70–85, 86–100)[6] and Chrispin–Norman score (0–10, 11–20, >20).[7]

TRIAL PROTOCOL

In the treatment group patients received a course of intravenous antibiotics for two weeks on entry to the trial.[8] Normally, a combination of tobramycin and a ureido-penicillin was used but in cases of resistance to these antibiotics an alternative was used, for example ceftazidime. Courses of intravenous antibiotics were repeated every four months until the IgG titre returned to the control range. If the IgG titre returned to the control range after treatment, the titre was checked every two months. If the titre subsequently rose to values above the control range, a two week course of intravenous antibiotics was given immediately and repeated at intervals of four months until the titre returned to the control range.

In the observation group patients received their usual treatment for cystic fibrosis which includes long term antistaphylococcal treatment, regular physiotherapy, high energy diet, and supplements of pancreatic enzymes and vitamins.

If significant symptoms developed in *any* patient in the study, which were considered to be associated with *P aeruginosa* infection, appropriate intravenous treatment was given according to our standard regimen.[8] If minor symptoms developed in any patient in the study, for example an increase in cough, or sputum production, considered to be due to other pathogens such as *Staphylococcus aureus* or

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Haemophilus influenzae then appropriate oral treatment was given.

On entry to the trial and at intervals of six months patients were assessed clinically in detail. Investigations included measurement of growth, respiratory function (peak expiratory flow rate, forced expiratory volume in one second (FEV$_1$), forced vital capacity), haemoglobin, white cell count (total and differential), erythrocyte sedimentation rate, plasma viscosity, C reactive protein, and serum IgG, IgA, IgM, and IgE concentrations. These were also measured at the beginning and end of every course of treatment. The serum IgG antipseudomonal titre was measured every two months and at the beginning and end of every course of treatment. Cultures of sputum and throat swabs were performed every month or more frequently if an infection was suspected or present.

STATISTICAL ANALYSES

The Student's *t* test and the Mann–Whitney U test were used. Significance levels were for two tailed tests.[9]

Results

Nineteen patients were enrolled into this trial. Clinical and laboratory parameters on entry for the observation and treated groups are shown in table 1.

Patients were developing early signs of chronic respiratory infection. Many had recently acquired a new persistent cough which had not settled despite courses of oral antibiotics. Chest radiographs showed early changes characteristic of cystic fibrosis with hyperinflation and some bronchial wall thickening. They had some impairment in respiratory function tests.

Table 1 Clinical data for patients on trial entry

	Observation group (n=12)	*Treated group (n=7)*
M/F	5/7	2/5
Age in years (range)	14 (6–29)	13 (7–19)
Mean (SD) Shwachman score	85 (3·6)	75 (4·0)
Range	75–90	55–95
Mean (SD) Chrispin–Norman score	6·0 (1·8)	10·1 (1·8)
Range	3–11	5–18
Mean (SD) weight for height (% predicted)	87·0 (1·8)	90·0 (0·8)
Range	76–97	75–94

Results presented in table 2 show that on entry to the trial the treated group had worse FEV$_1$, serum IgG antipseudomonal titre, and serum IgG concentration than the observation group. After one year in the trial these parameters had improved in the treated group and deteriorated in the observation group. The annual rate of increase of serum IgG antipseudomonal titre was 520 in the observation group while it decreased by 125 in the treated group. FEV$_1$ predicted remained constant in the observation group over one year but improved by 11% in the treated group. Serum IgG concentration increased in the observation group but remained unchanged in the treated group.

The proportion of respiratory cultures that were positive for *P aeruginosa* in the observation group increased from 62% in the three months immediately preceding entry to 93% in the period 12 months after entry. The proportion of pseudomonal isolates which were mucoid increased from 14% to 39% in the same period. In contrast, the proportion of cultures which were positive for *P aeruginosa* and the proportion of pseudomonal isolates which were mucoid remained essentially unchanged in the treated group. After one year the proportion of *P aeruginosa* positive cultures and the proportion of mucoid isolates were significantly lower in the treated than the observation group ($p<0{\cdot}001$ and $p<0{\cdot}10$ respectively).

Discussion

This trial was designed to test our preliminary findings that an increased antipseudomonal antibody titre was an early sign of pseudomonal infection of the respiratory tract which, in many patients with cystic fibrosis, precedes isolation of the organism from the respiratory tract.[2–4] It was also designed to determine whether very early antipseudomonal treatment (that is before the organism has been isolated and during the first few months of its isolation) would delay the clinical deterioration associated with pseudomonal infection. We therefore excluded patients who had an IgG titre of >2000 as earlier studies suggested that by this stage infection was chronic and irreversible.[2–4]

Treated patients have progressed better than the observation group in every parameter

Table 2 Clinical and laboratory parameters for patients on trial entry and after one year

	On entry			*After one year*		
	Observation group (n=12)	*Treated group (n=7)*	*p Value*	*Observation group (n=12)*	*Treated group (n=7)*	*p Value*
Serum IgG titre	685	805	NS	1205	680	<0·05
Range	260–1400	330–1363		390–5200	260–1915	
FEV$_1$ (% predicted)	75	67	NS	75	78	NS
Range	64–94	47–102		41–92	55–110	
WCC ($\times 10^9$/l)	7·9	8·8	NS	7·5	7·7	NS
Range	5·3–14·7	5·0–13·8		6·0–9·9	5·0–11·6	
% Neutrophils	51	59	NS	54	61	NS
Range	41–70	44–83		44–71	49–75	
Serum IgG (g/l)	9·5	13·97	<0·10	11·3	13·3	NS
Range	6·0–13·4	8·0–20·5		6·9–14·0	6·0–20·6	
% Cultures positive:						
Non-mucoid *P aeruginosa*	62	49	NS	93	51	<0·001
Mucoid *P aeruginosa*	14	9	NS	39	7	<0·10
No of courses antipseudomonal treatment/patient				1·09	2·8	

WCC=white cell count.

studied. There was a significant difference during the study period in changes in the treated and observation groups in serum IgG titre, FEV_1, serum IgG concentrations, and in the proportion of pseudomonas positive respiratory cultures.

We conducted a similar trial with patients from whom *P aeruginosa* had not yet been isolated but who had specific antibody titres greater than the control range. These patients were normally asymptomatic and respiratory cultures normally grew no pathogens. The Chrispin-Norman *x* ray scores were 80–95 (mean 88) and 90–95 (mean 93) in the observation and treated groups respectively. FEV_1 (% predicted) was 65–116 (mean 86) and 79–88 (mean 83) in the observation and treated groups respectively.

Patients in this second trial were initially in a very good clinical state and changes in clinical parameters were small during the study period, so differences between the observation and treated groups were not statistically significant. There was, however, a similar pattern to that seen in the larger trial: a deterioration in the observation group and improvement or no change in the treated group. After six months in the trial, serum IgG antipseudomonal titres had increased in the observation group to 360–700 (mean 374) from 300–540 (mean 327) on entry but had decreased slightly in the treated group to 187–320 (mean 260) from 273–350 (mean 296) on entry.

The need for regular venepuncture to check antibody titres caused distress among some of the patients. Future monitoring of values could be done by finger prick sampling which has been shown to be adequate for detecting serum IgG to antibodies to *P aeruginosa* and may be more acceptable to some parents and patients.[10] Admissions for courses of intravenous antibiotic treatment, particularly in relatively well patients, inevitably caused some disruption to family life. The oral antipseudomonal antibiotic ciprofloxacin became available during the study and was a major factor leading to the premature discontinuation of these trials. Ciprofloxacin has been shown to be as effective as a course of intravenous antibiotics in one study,[11] while other work shows ciprofloxacin to be comparable in mildly affected patients but less effective in severely affected patients.[12]

This trial has confirmed the value of IgG antipseudomonal antibody measurement in monitoring the development and treatment of patients with cystic fibrosis with early respiratory infection. Early and repeated antipseudomonal antibiotic treatment appears to be beneficial for these patients. We intend to continue monitoring antibody titres in our patients and treating early infection with courses of oral antipseudomonal antibiotics.

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Archives of Disease in Childhood 1992; **67**: 1089–1092

Management of hypertensive emergencies

J E Deal, T M Barratt, M J Dillon

Abstract

Between 1975 and 1985, 454 patients with hypertension were admitted to the Renal Unit of the Hospital for Sick Children. A total of 110 (24%) patients presented with severely raised blood pressures deemed to require emergency management. At presentation 84/110 had symptoms and signs of long standing hypertension with neurological involvement. Between 1975 and 1980 bolus intravenous injections of diazoxide and/or hydralazine were used with the aim of reducing the blood pressure to within the normal range for age in the first 12–24 hours after admission. Of 57 patients treated in this way 13 developed hypotensive complications and four, whose blood pressures returned to normal within 24 hours of admission, suffered irreversible neurological damage. Subsequently the management changed to the use of intravenous infusions of labetalol (1–3 mg/kg/hour) and/or sodium nitroprusside (0·5–8 μg/kg/min) to enable a more gradual controlled reduction of blood pressure over the first 96 hours of admission. Between 1980 and 1985, 53 patients were treated using this regimen. In all cases blood pressure reduction was achieved in a more controlled manner without further neurological impairment or serious irreversible side effects.

From our experience, the use of labetalol and sodium nitroprusside by incremental infusion in the critical early phase of management has resulted in improved control of accelerated hypertension without the sudden hypotensive episodes seen when bolus injections are used.

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There is a tendency in the treatment of hypertensive emergencies, supported by many textbooks and leading articles, to aim for as fast a reduction in blood pressure as possible in order to avoid the potentially dangerous and life threatening complications of high blood pressure. Many textbooks still advocate rapid blood pressure reduction using bolus treatment with intravenous or intramuscular injections of antihypertensive drugs and, more recently, sublingual preparations aiming to bring the blood pressure down to normal levels as quickly as possible. However, Ledingham and Rajagopalan reported in 1979 the occurrence of permanent neurological deficits in adults treated with bolus antihypertensive therapy resulting in rapid blood pressure reduction.[1] As a result they advocated the use of controlled blood pressure reduction by the use of infusion treatment. Permanent neurological damage has also been reported in children treated for hypertension[2 3] and infusion treatment has been advocated for the treatment of accelerated hypertension in them.[4] We therefore reviewed our treatment of hypertensive emergencies and report here our experience over 10 years comparing the use of bolus treatment and incremental intravenous infusion treatment in children.

The level of systolic or diastolic blood pressure at which children who are at risk of hypertensive complications can be distinguished from those who are not at risk can not of itself be defined. Symptoms and signs of a hypertensive emergency are non-specific and the assessment of the need for urgent treatment depends upon a clinical assessment of the degree and rate of rise of blood pressure and the potential for end organ damage or loss of life in each individual child. Severe hypertension is defined as a blood pressure greater than the 99th centile for age and sex. Accelerated hypertension has been defined as a blood pressure greater than the 95th centile for age and sex in which there is evidence of end organ damage or dysfunction with fibrinoid necrosis of arterioles and signs of grade III hypertensive retinopathy.[5]

Patients and methods

Before 1980 children presenting with a hypertensive emergency to our unit were treated with bolus intravenous diazoxide (3–5 mg/kg/dose) and/or intramuscular hydralazine (0·2–0·4 mg/kg/dose) aiming for as rapid a reduction in blood pressure to normal as was possible. Since 1980 children with a hypertensive emergency have been managed with incremental intravenous infusions of labetalol and/or sodium nitroprusside, aiming to reduce the blood pressure in the first 24 hours by only a third of the eventual blood pressure reduction desired. The target blood pressure was the 95th centile systolic value for age and sex for each child obtained from the American Task Force data.[5]

Between 1975 and 1985, 454 children who were referred to the Renal Unit at the Hospital for Sick Children, London were hypertensive. A total of 110 (24%) presented with severe hypertension deemed to require emergency management. Fifty seven presented between 1975 and 1980 and received bolus treatment, and 53 presented between 1980 and 1985 and received infusion treatment. These two groups of children were reviewed retrospectively and the outcome and any complications of treatment compared.

Details of the two groups are shown in table 1. Group 1 received boluses of diazoxide (3–5 mg/kg/dose intravenously) and/or hydralazine (0·2–0·4 mg/kg/dose intramuscularly) until their blood pressure had returned to 'normal'. Group 2 were treated with incremental intravenous infusions of labetalol (1–3 mg/kg/hour) and/or sodium nitroprusside (0·5–8 μg/kg/min) aiming for a third of the eventual blood pressure reduction desired in the first 24 hours. The dose of labetalol or sodium nitroprusside was titrated in increments according to the child's blood pressure. Normal saline was administered in boluses of 50 ml if the blood pressure fell below the lower limit of blood pressure that had been set for each child. The blood pressure was measured by nursing staff at 5 minute intervals while the infusion was running and at 15 minute intervals when the infusion was temporarily discontinued; changes in the infusion rate were only made after two consistent readings of blood pressure had been obtained. Neurological observations including pupillary responses to light were recorded regularly. Labetalol was avoided in any child who had signs of cardiac failure and/or had a history of asthma. Monitoring of plasma cyanide concentrations of those children who received sodium nitroprusside for longer than 48 hours was performed and no signs of toxicity occurred in our patients.

Results

Children in both treatment groups were comparable in terms of age, initial blood pressure, and underlying diagnosis (tables 1 and 2). Altogether 84/110 children at presentation had symptoms and signs suggestive of accelerated hypertension (44 in the bolus group, 40 in the infusion group) with end organ damage such as hypertensive retinopathy and/or left ventricular hypertrophy. They all gave histories of symptoms attributable to hypertension, for example headaches and visual problems, that had been present for weeks or months before admission. Their admissions were often prompted by the development of neurological symptoms and signs (table 3): 28 of the children presented with hypertensive encephalopathy. Although more group 1 children had a facial palsy or signs of a hemiplegia at presentation, the differences were not statistically significant. Twenty six of the 110 did not have evidence of sustained hypertension but had severely raised blood pressures and were treated with parenteral therapy to prevent the occurrence of acute hypertensive complications.

Fifty seven children were treated with intravenous diazoxide, 16 of these also received intramuscular hydralazine. Thirteen of the 57 children in group 1 developed hypertensive complications associated with the rapid reduction of their blood pressures (see table 4). In nine these complications were transient with recovery of visual and renal function to pretreatment levels, but in four patients the neurological damage sustained during treatment was permanent (table 5).[2 3] These four patients were all subsequently diagnosed as having reflux nephropathy. Only one of them had previously had urinary tract infection diagnosed and none was previously known to have renal impairment. On admission they were all severely hypertensive with long standing hypertensive symptoms and evidence of sustained disease with end

Table 1 Clinical details of 110 children treated for accelerated hypertension. Results are mean (SD)

	Group 1 (n=57)	Group 2 (n=53)
Age (years)	8·04 (4·15)	7·97 (4·53)
Range	0·08–14·58	0·08–17·00
Systolic blood pressure (mm Hg)	181 (40·5)	179 (37·1)
Range	115–300	120–260
Diastolic blood pressure (mm Hg)	127·0 (34·3)	127·5 (36·5)
Range	80–230	60–215
Male:female	33:24	31:22

There were no significant differences between the variables by Student's *t* test.

Table 2 Causes of hypertension in 110 children treated for accelerated hypertension between 1975–1985

Diagnosis	Group 1 (n=57)	Group 2 (n=53)
Reflux nephropathy	16	12
Obstructive uropathy	7	5
Renovascular disease	6	10
Glomerular disease	10	8
Polycystic renal disease	1	2
Haemolytic uraemic syndrome	2	6
Coarctation	2	2
Phaeochromocytoma	0	2
Wilms' tumour	2	0
Renal dysplasia	3	2
Miscellaneous	8	4

Table 3 Symptoms and signs at presentation

	Group 1 (n=57)	Group 2 (n=53)
Visual symptoms	6	4
Facial palsy	9	4
Convulsions	15	13
Hypertensive retinopathy	16	14
Hypertensive encephalopathy	15	13
Hemiplegia	6	3
Left ventricular hypertrophy	9	5
Cranial bruits	2	4
Blood pressure >99th centile without end organ damage	13	13

Table 4 Signs and symptoms developed during emergency treatment of hypertension

Complication	Group 1 (n=13)	Group 2 (n=2)
Transient visual loss	6	0
Transient acute renal failure	5	2
Permanent visual loss	4	0
Transverse ischaemic myelopathy	1	0

Table 5 Details of four patients with permanent neurological damage

Patient No	Blood pressure change in first 24 hours (mm Hg)	Complication
1	$\frac{260}{190}\rightarrow\frac{120}{60}$	Permanent bilateral visual field losses
2	$\frac{285}{230}\rightarrow\frac{90}{60}$	Permanent bilateral visual field losses; transient acute renal failure; transverse ischaemic myelopathy
3	$\frac{200}{130}\rightarrow\frac{160}{80}$	Permanent unilateral visual loss; bilateral VIth nerve palsies
4	$\frac{280}{190}\rightarrow\frac{120}{90}$	Permanent bilateral visual loss

organ changes, that is hypertensive retinopathy and left ventricular hypertrophy. Three of these four patients had a facial palsy present before admission that had not been investigated and all were encephalopathic. Their hypertension was successfully treated with intravenous boluses of diazoxide but with the reduction in their blood pressures they showed deterioration in their neurological signs with loss of pupillary light responses and decreased levels of consciousness. One child also developed transient acute renal failure requiring peritoneal dialysis and developed a transverse ischaemic myelopathy. Despite stellate ganglion block to improve ciliary artery blood flow and measures to raise the blood pressure in all four patients there was no improvement in visual or neurological function. Subsequent investigations showed evidence of anterior ischaemic optic neuropathy.[3] All four patients are now severely visually handicapped and one is also paraplegic.

Fifty three children were treated with incremental hypotensive infusions: 25 with labetalol alone, 12 with sodium nitroprusside alone because of concern for their cardiac function or a history of reversible airway disease, or the need for a vasodilator in addition to an antihypertensive agent, and 16 children received both labetalol and sodium nitroprusside because of difficulties controlling their blood pressure with a single agent. Only two of these 53 children developed hypotensive complications: transient acute renal failure which required peritoneal dialysis. No patients developed new neurological signs or visual problems and no hypertensive complications occurred once treatment had started. Blood pressure control was achieved in all patients with clinical improvement of their hypertensive signs and symptoms. Infusions were well tolerated, but intensive nursing was required, particularly during the first three days of admission, to achieve a smooth, controlled reduction in blood pressure.

Discussion

These results show that hypertensive emergencies in children can be successfully treated by incremental infusion treatment. Bolus treatment and rapid blood pressure reduction was associated with a higher incidence of permanent neurological sequelae and should therefore be avoided in any child who presents with severe hypertension, particularly if there are symptoms and/or signs suggestive of long standing hypertension. These two groups of children had similar signs and symptoms at presentation and had similar degrees of hypertension. Differences between the groups occurred in the rapidity with which the blood pressures were reduced and the treatment methods that were used to achieve this. Children managed by incremental infusion were monitored much more closely during their treatment so that sudden drops in blood pressure did not occur and any changes in neurological signs were quickly appreciated.

Some children in both groups already had signs of neurological damage, secondary to their hypertension, at presentation. Further deterioration in neurological status was associated with the rapid and uncontrolled blood pressure reduction that occurred with the use of bolus treatment, no permanent sequelae being seen in the children managed with infusion hypotensive treatment. Although there were no statistically significant differences between the children in groups 1 and 2 in the incidence of neurological signs and symptoms at presentation, it may be that children in group 1 had longer standing hypertension and hence were more prone to the development of hypotensive complications.

There is a recognised association between the presence of renal artery stenosis and arterial disease affecting the cerebral circulation,[6] which might account for an increased risk of complications occurring with blood pressure reduction; however, more children in group 2 were found to have renovascular disease than in group 1.

In severe hypertension from whatever cause, initial vasoconstriction occurs with subsequent arteriolar fibrinoid necrosis, blood vessel wall thickening and fibrosis, hypertrophy of the intima and media, and loss of relative elasticity with a subsequent reduction in intraluminal diameter.[7] After a while the vessel changes become fixed and blood vessels cannot easily dilate or react to changes in blood flow, especially relative hypotension. These changes are particularly important in the cerebral vasculature with loss of cerebral blood flow autoregulation.[8] If blood pressure in that situation is rapidly reduced the cerebral vasculature cannot dilate to ensure adequate cerebral perfusion and ischaemia occurs, particularly of watershed areas of the cerebrum and cerebellum such as the visual cortex and areas supplied by end arteries in the central nervous system, for example spinal arteries and ciliary arteries supplying the optic nerve. Although there are justifiable concerns to prevent the complications of hypertension such as cerebral haemorrhage, too rapid blood pressure reduction can be more harmful in a circulation that has 'adjusted' to the hypertensive state.

The key to safe blood pressure reduction is probably not which drug is used but its method of administration and the rapidity with which blood pressure falls. Frequent monitoring of the child's blood pressure, as it is reduced, so that the blood pressure can be quickly raised using intravenous saline should relative hypotension occur; monitoring of pupillary responses to detect the first signs of visual compromise; and slow controlled blood pressure reduction are all vital to the successful treatment of hypertensive emergencies. Incremental infusion treatment allows these criteria to be met. Bolus treatment by whatever route is dangerous if the blood pressure is not monitored adequately as unpredictable and sustained drops in pressure can occur.

Sublingual nifedipine has been increasingly advocated for use in hypertensive emergencies,[9 10] but as with bolus diazoxide or hydralazine its effect and duration of action are unpredictable and similar hypotensive complications could occur.[11] The use of sublingual nifedipine, administered without intravenous access in severe hypertension, cannot be recommended for these reasons, although it may have some role if appropriate precautions are taken.

More recently oral and sublingual captopril have been reported to be effective in hypertensive emergencies with few side effects.[12 13] Children have a more active renin-angiotensin system than adults[14] and a higher incidence of renal artery stenosis as a cause of severe hypertension,[15] both of which contraindicate the use of an angiotensin converting enzyme inhibitor as first line treatment when the underlying cause and disease duration are unknown. Oral captopril, however, has been reported to be effective in a child with haemolytic uraemic syndrome in whom the hypertension was acute and resistant to treatment with other antihypertensives.[16] The use of other oral drugs might allow blood pressure to be reduced gradually but in children with accelerated hypertension drug absorption, onset of action, and duration of action are all unpredictable and the use of the oral route would not obviate the need for close monitoring and intravenous access to allow rapid blood pressure elevation with saline infusion should relative hypotension occur.

The use of incremental infusions of labetalol for the treatment of accelerated hypertension has been reported to be effective in adults without hypotensive complications,[17 18] but no reports exist of its use in the emergency management of children. Sodium nitroprusside has been used for the treatment of severe hypertension in adults and children with good clinical effect and without hypotensive complications or problems with cyanide toxicity.[19 20] The use of incremental infusions, however, requires skilled nursing care and frequent monitoring of blood pressure. The onset of accelerated hypertension is a medical emergency and such labour intensive treatment is justified in order to prevent both further hypertensive and hypotensive complications.

The incidence of severe and accelerated hypertension has decreased over the last 10 years with increasing recognition of the early signs and symptoms of high blood pressure in childhood. Better recognition, investigation, and management of children with a history of urinary tract infections, follow up of children with renal disease and reflux nephropathy, and the appreciation of the diverse way in which hypertension can present in the young should prevent children from presenting with a hypertensive emergency. However, when a child with severe hypertension does present, a careful clinical assessment particularly noting any signs or symptoms indicative of long standing hypertension and any features suggestive of renovascular disease and associated intracerebral vascular disease should be identified as well as signs of end organ damage and impending cardiac failure. Only then can the decision be made concerning the rapidity of blood pressure reduction and the most appropriate drugs to be used. In any child with sustained severe hypertension, particularly with neurological symptoms and signs, we would recommend that the blood pressure should be reduced by incremental infusion of short acting drugs such as labetalol or sodium nitroprusside lowering the blood pressure in a controlled manner over the first 96 hours of admission and avoiding the unpredictable, relative hypotension seen with bolus treatment and thereby maintaining adequate cerebral and renal blood flows.

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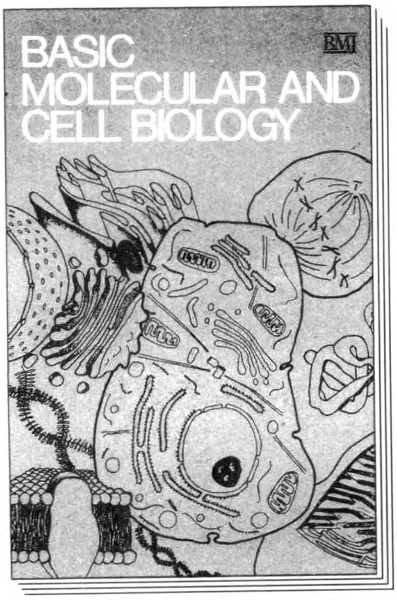

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Archives of Disease in Childhood 1992; **67**: 1093–1094

Early thrombocytopenia in HIV infection

R M Beattie, J Q Trounce, E G Hermione Lyall, D M Gibb

Abstract

Three children aged between 7 months and 2 years developed thrombocytopenia as an early feature of HIV infection. The prevalence of this condition, possible pathogenesis, and options for treatment are discussed. HIV testing should be considered in the investigation of a child with thrombocytopenia.

(*Arch Dis Child* 1992;67:1093–4)

As the incidence of HIV infection in children increases[1] and the various manifestations of the disease become apparent through studies of its natural history[2] it is clear that it needs to be considered in the differential diagnosis of many childhood diseases. We report here a series of children with HIV infection who presented with thrombocytopenia.

Case reports

CASE 1

A healthy 12 month old boy was referred to hospital with a five month history of bruising in areas of accidental trauma. He had no other abnormalities on clinical examination, was thriving, and was developmentally normal.

Laboratory investigation showed a platelet count of $8\times10^9/l$. The blood film was normal and his bone marrow showed an increase in megakaryocyte numbers consistent with peripheral platelet destruction. An initial diagnosis of idiopathic thrombocytopenic purpura was made. Only later was HIV considered in the differential diagnosis and after counselling the parents the child was tested. Tests for antibodies to HIV and the p24 antigen were positive. The CD4 count was low for his age with a reversal of the CD4:CD8 ratio, and hyperglobulinaemia was present. On the basis of these results a diagnosis of HIV infection with thrombocytopenia was made. His platelet count showed a good but temporary increase after treatment with intravenous immunoglobulin at a dose of 1 g/kg for two days. He has continued to receive this four times a week for six months.

Treatment with zidovudine (3′-azido-3′-deoxythymidine) for six months has not resulted in any permanant increase in platelet count and a trial of steroids by mouth was given. He became hyperactive and as there was no improvement in his platelet count they were stopped after three weeks. He has continued to have regular intravenous immunoglobulin treatment. He has no other manifestations of HIV infection.

The parents had no history of high risk behaviour for HIV infection but were subsequently shown to be positive for antibodies to HIV. The father's platelet count was $22\times10^9/l$ at presentation.

CASE 2

A 21 month old boy who had had a heart operation at the age of 4 months presented with a short history of bruising and had a platelet count of less than $10\times10^9/l$.

The bone marrow examination showed an increase in megakaryocyte numbers and a presumptive diagnosis of idiopathic thrombocytopenic purpura was made. There was no response to three courses of intravenous immunoglobulin and treatment with steroids was begun. Prednisolone was given at an initially high dose (2 mg/kg), decreasing slowly after two weeks to 5 mg on alternate days to keep the platelet count between 50 and $100\times10^9/l$.

At the age of 4 years (more than three years later) the child was found by donor tracing to have received a blood transfusion from donor positive for antibodies to HIV and subsequent testing showed the child to be infected with HIV. In addition to the thrombocytopenia he has since developed lymphocytic interstitial pneumonitis, encephalopathy, and is unwell. He currently receives regular intravenous immunoglobulin and prednisolone and zidovudine on alternate days. His platelet count has remained greater than $90\times10^9/l$.

CASE 3

A boy aged 7 months presented with petechiae and a platelet count of $6\times10^9/l$. His mother was known to be infected with HIV following a blood transfusion.

The T lymphocyte subsets were abnormal with reversal of the CD4:CD8 ratio and the p24 antigen was positive, indicating HIV infection. He received a short course of steroids which had no effect on the platelet count. A temporary increase in the platelet count occurred after intravenous immunoglobulin at a dose of 2 g/kg. The family then moved overseas. Regular treatment with intravenous immunoglobulin was recommended but not given. One year later, however, on returning to the United Kingdom his platelet count had recoverd spontaneously without treatment.

He is currently well but remains positive for the p24 antigen and the CD4 count is slowly decreasing.

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Discussion

Chronic thrombocytopenia in childhood and an approach to its management has been reviewed by Chessells.[3] Isolated thrombocytopenia can be the presenting feature of HIV infection in childhood as shown by the cases reported here and elsewhere.[4,5] It should be included in the differential diagnosis of thrombocytopenia in an otherwise well child.

Thrombocytopenia is well recognised as a manifestation of HIV infection in adults and children. In adults with asymptomatic HIV infection the prevalence of thrombocytopenia (defined as a platelet count of less than $100 \times 10^9/l$) has been reported to be 3–12%; higher prevalences of up to 30% have been found in adults with AIDS.[6] Of the children known to have HIV infection or AIDS in the United Kingdom about 10% are thrombocytopenic (C Davison, personal communication, British Paediatric Surveillance Unit). Higher prevalences have been reported in more selected groups of children with symptomatic HIV infection.[7]

Thrombocytopenia in HIV infection and AIDS is multifactorial and its aetiology and pathogenesis in adults has been described elsewhere.[8] In the children described here (cases 1 and 2) the presence of bone marrow hyperplasia suggests peripheral platelet destruction. The likely mechanism is the deposition of immune complexes on the platelet Fc receptor with its subsequent uptake by phagocytes and destruction as in adult idiopathic thrombocytopenic purpura. Platelet antibodes have been reported in adults with HIV infection and thrombocytopenia.[9]

The major danger of HIV associated thrombocytopenia is cerebral haemorrhage and this has been reported.[5,10] Spontaneous remission may occur (as in case three) and has been described in adults and children.[5,11] If the platelet count is less than $20 \times 10^9/l$ there is a risk of bleeding and treatment is indicated. The treatment options include zidovudine, intravenous immunoglobulin, steroids, and splenectomy.

Zidovudine is known to increase the platelet count in HIV infected adults[12] and has been used effectively in the treatment of HIV associated thrombocytopenia. A response in 68% of adults has been reported, though treatment for over three months was required in some before an increase in the number of platelets was seen.[13]

Intravenous immunoglobulin has been found to be of value in HIV associated thrombocytopenia[4] and it resulted in an improvement in the platelet count in two of the three children reported here. As a regular treatment (case 1), however, it does require regular cannula insertion and is expensive.

Prednisolone was effective in one of the two children in whom it was used. In the second its use was curtailed because of hyperactivity. The treatment of HIV associated thrombocytopenia in children with prednisolone has been reported by Ellaurie *et al* with success in five of seven cases.[5] An appropriate regimen would be 2 mg/kg/day initially decreasing after a response has been seen to the lowest possible alternate day maintainance dose.[14] There are concerns about using steroids in a disease where immunity is already suppressed and the incidence of infections is increased. Adverse effects have not been reported with the use of steroids in other diseases such as *Pneumocystis carinii* pneumonia associated with HIV infection in adults, however.[15]

Splenectomy has been reported to increase the platelet count in some adults with HIV associated thrombocytopenia.[16] Its use in infants, however, would not be justified except as a last resort because of the subsequent adverse effects on immunity and the associated risk of sepsis particularly with *Streptococcus pneumoniae*.

In conclusion we stress the importance of considering HIV in the differential diagnosis of thrombocytopenia in children. The absence of symptoms or risk factors should not preclude suspicion of HIV infection.

In children with HIV associated thrombocytopenia treatment is indicated if the platelet count is low. Further investigation into the pathogenesis of the condition and the most appropriate forms of treatment for children is required.

We thank Dr J Y Q Mok for allowing us to report case 2.

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Thymopentin treatment in severe atopic dermatitis–clinical and immunological evaluations

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Abstract

An open clinical trial of thymopentin was conducted on 16 children with severe atopic dermatitis. The patients were treated with injections three times a week of 50 mg thymopentin for six weeks. They were then divided randomly into two groups: group A continued thymopentin for an additional six weeks, and group B were treated with normal saline. Clinical parameters and immunological function were evaluated serially. The total severity score started to decline from baseline significantly three weeks after treatment, and continued throughout the study period in group A but began to flare up in group B two weeks after stopping thymopentin. All the eight patients in group A completed the trial but three out of eight in group B dropped out because of flaring up of skin lesion. In vitro production of interleukin-4 tended to decrease and that of interferon gamma tended to increase, but total serum IgE, in vitro IgE synthesis, and abnormally low CD8+ CD11b+ suppressor T cells remained unchanged. Histamine releasing factor (HRF), plasma histamine, and respiratory burst activities of polymorphonuclear leucocytes were appreciably decreased after thymopentin treatment.

It is concluded that the clinical efficacy of short term thymopentin treatment very possibly results from the decreased production of HRF and decreased release of polymorphonuclear leucocyte derived inflammatory mediators and may have no relation with antigen-IgE immune reaction.

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Atopic dermatitis is a chronic cutaneous inflammatory disease characterised by early age of onset, severe pruritus, typical morphology and distribution of skin rash, chronic relapsing course, and personal or family history of atopy.[1 2] It is a common disease among infants and children with an incidence of 1·9% to 8·3% in white people[3–6] and 1·24% in Chinese schoolchildren.[7] Chronic atopic dermatitis may result in significant morbidity, including hospitalisation for control of skin disease and infection, lost school days, psychological trauma from physical disfigurement, and occupational disability. The management of atopic dermatitis has been less than satisfactory. None of the currently available treatments are curative and treatment is empirical.[6]

Although the pathogenesis of atopic dermatitis remains unclear, a number of immunological abnormalities have been described. They include:

(i) Raised and sustained serum IgE concentrations,[8]

(ii) Impaired T cell function,[9]

(iii) Decreased natural killer cell activity,[10]

(iv) Defective capacity to generate alloreactive cytotoxic T cells,[11]

(v) Impaired autologous mixed lymphocyte reaction due to defective CD4 responder T cells[12]

(vi) Increased cell mediated cytotoxicity against skin fibroblasts,[13]

(vii) Most importantly, immunological reconstitution after bone marrow transplantation results in the permanent resolution of eczema in Wiskott-Aldrich syndrome, a primary T cell immunodeficiency with raised serum IgE, providing in vivo evidence that immune defects predispose to the development of eczema.[14]

Thymopoietin is a polypeptide hormone of the thymus, originally isolated from bovine thymus extract by its effect on neuromuscular transmission.[15] It is secreted by thymic epithelial cells and has been shown to influence both the differentiation of thymocytes[16] and the function of mature T cells.[17 18] Thymopentin (Timunox, Immunobiology Research Institute, Annandale, NJ) is the active pentapeptide (Arg-Lys-Asp-Val-Tyr) moiety corresponding to amino acids 32 to 36 of the linear 49 amino acid sequence of thymopoietin. The biological effects of thymopentin mimic those of thymopoietin in all systems in which it has been evaluated.[18 19] It was marketed in Italy in 1985, in Belgium in 1987, and in Germany in 1988, and has been used in a number of diseases in which T cell deficiency may have a role.[20]

Recent studies suggest that thymopentin influences IgE synthesis,[21] and it might therefore influence the course of atopic diseases in man. Recently, clinical improvement with thymopentin that produced reductions in overall severity in patients with atopic dermatitis has been reported,[22 23] but the working mechanisms have not been studied extensively. We present the clinical efficacy of an open trial of thymopentin in children with severe atopic dermatitis and correlate the clinical efficacy with the in vivo and in vitro immunological changes after thymopentin treatment.

Subjects and methods

SUBJECTS

Sixteen children, nine boys and seven girls, aged 3 to 14 years, were enrolled into this study.

The clinical trial was approved by the human research committee of this hospital and informed consent was obtained for each patient. All of the patients had severe pruritus, skin lesions of characteristic morphology and distribution, chronic relapsing course, and a history of atopy, which met the criteria for the diagnosis of atopic dermatitis.[1 2] The age of onset ranged from 1 month to 1 year, the mean (SD) duration of atopic dermatitis was 8·6 (3·0) years, the serum IgE concentrations ranged from 224 to 5241 IU/ml (mean (SD) 2318 (1525) IU/ml), and the mean (SD) area of involved body surface was 81·5 (25·0)%. The severity was graded on a scale of 0–3 for each of the five parameters: erythema, pruritus, oedema/papulation, excoriation, and scaling/dryness. To be enrolled the patient had to have a severity score of 6 or higher (including a score of 2 or more for both erythema and pruritus). The mean (SD) total severity score before treatment was 14·4 (0·9) (range 12–15). Twenty healthy schoolchildren, aged 7 to 15 years, were included as controls for immunological study.

TREATMENT PROTOCOL

After enrolment the patients received three subcutaneous injections each week of 50 mg of thymopentin for a consecutive six weeks. The patients were then divided randomly into two groups. One group (group A) continued the thymopentin treatment for an additional six weeks, and the other group (group B) was injected with normal saline. Both groups were comparable regarding age, severity score, and serum IgE concentration. During the treatment patients were allowed to continue antihistamines and topical corticosteroids, but systemic corticosteroids were discontinued for at least four weeks before the study. No recommendation on food restriction and environmental control was made.

EVALUATION

The patients were seen every week by one author (KHH). Dermatological assessment, routine laboratory tests (blood chemistry, haematology, and urinalysis), and immunological tests were performed before and at the end of the third, sixth, and 12th week after treatment. The clinical response was evaluated by a dermatologist who did not know the treatment protocol, and adverse reactions were observed carefully. Parents' satisfaction was recorded.

IMMUNOLOGICAL TESTS

Enumeration of lymphocyte subpopulation

T cell subsets were enumerated by FACscan (Becton-Dickinson), using the monoclonal antibodies shown in table 1.

Preparations of sera and culture supernatants

Peripheral blood mononuclear cells (MNCs) were obtained by Ficoll/Hypaque gradient density centrifugation. MNCs at a concentration of 2×10^6 cells/ml in complete culture medium (Roswell Park Memorial Institute-1640 supplemented with 10% heat inactivated fetal calf serum, antibiotics and L glutamine) were stimulated with 2 μg/ml phytohaemagglutinin (PHA) (Wellcome) for three days and the supernatants were collected by centrifugation and stored at −20°C until testing.[24 25] The above mentioned culture conditions, including cell density, PHA concentration, and days of cultivation, were found to be optimal for cytokine production in our previous studies.[24–26]

Table 1 Monoclonal antibodies used to enumerate lymphocyte subpopulations

CD3 (total T cells)
CD19 (total B cells)
CD3−CD16+CD56+ (natural killer cells)
CD4 (helper/inducer)
CD4+CD45RA+ (suppressor/inducer)
CD4+CD45R− (helper/inducer)
CD8+ (suppressor/cytotoxic)
CD8+CD11b+ (suppressor)
CD8+CD11b− (cytotoxic)
CD3+CD25+ (activated CD3)
CD4+CD25+ (activated CD4)
CD8+CD25+ (activated CD8)
CD3+HLA−DR+ (activated CD3)
CD4+HLA−DR+ (activated CD4)
CD8+HLA−DR+ (activated CD8)

Measurements of soluble interleukin (IL)-2R, CD4 molecule, and cytokines in supernatants

Cell free CD4 and IL-2 receptor tests kits were purchased from T Cell Sciences (Cambridge, MA), IL-2 and interferon gamma test kits from Genzyme (Boston, MA), and IL-4 and IL-6 test kits from R and D System (Minneapolis, MN). The principle of those tests was sandwich enzyme immunoassay (ELISA), using two monoclonal antibodies against different epitopes of the target molecule (CD4, IL-2, and IL-2R) or monoclonal antibody (first) followed by polyclonal antibody (IL-4, IL-6, and interferon gamma). The sensitivity of the ELISA was 50 pg/ml for IL-2, 50 U/ml for IL-2R, 12 U/ml for CD4, 3 pg/ml for IL-4, 3·5 pg/ml for IL-6, and 100 pg/ml for interferon gamma. The interassay variation of all tests were around 5–10% and a similar figure was found for intra-assay. All the samples of a single individual were run in duplicate simultaneously and at least one normal control was included in each experiment.

Measurement of histamine releasing factor (HRF) activity

HRF was measured as previously described.[27] MNCs (2×10^6 cells/ml) were stimulated with 2 μg/ml PHA for four hours, washed, and incubated for additional 20 hours. The supernatant was collected, concentrated 50-fold, using a YM-5 Amicon membrane. The HRF activity of the supernatant was measured by its capacity to release histamine from basophils obtained from a healthy high HRF responder and was expressed as percent of total cellular histamine released. The histamine was determined by using histamine radioimmunoassay kits (Immunotech, France). The sensitivity of the kit was 0·5 nmol/l.

Measurement of serum IgG, IgA, IgM, and IgE

The IgG, IgA, and IgM were measured by nephelometry (Beckman). In vitro production of IgE was done according to the method of Saryan *et al.*[18] The IgE concentrations in sera and culture supernatants were measured by Phadebas IgE PRIST kits (Pharmacia).

Lucigenin amplified chemiluminescence assay

Chemiluminescence was assayed by the method of Gyllenhammar,[29] using a luminometer (model 1251, LKB, Bromma) and recorded as mV. Reaction mixtures contained 1×10^6 neutrophils, 0·1 mg lucigenin, and 40 ng phorbol myristate acetate (PMA) or 1 mg opsonised zymosan; and Hanks' balanced salt solution (HBSS) was added up to a final volume of 1 ml in each reaction. The readings were started two minutes after the addition of reagents and were monitored every eight minutes up to an hour.

MEASUREMENTS OF SUPEROXIDE AND HYDROGEN PEROXIDE PRODUCTIONS

Superoxide production was measured as superoxide dismutase inhibitable reduction of ferricytochrome *c* with PMA or opsonised zymosan as stimulant.[30] Quantitation of hydrogen peroxide is based on the horseradish peroxidase dependent oxidation of phenol red with PMA or opsonised zymosan as stimulant.[31] For the superoxide assay the reaction mixture in each well consisted of ferricytochrome *c* (2 mg/ml), PMA (40 ng/ml), or opsonised zymosan (1 mg/ml) with neutrophils in the presence or absence of superoxide dismutase (300 U/ml). The microtitre plates were incubated and shaken at 37°C for one hour and absorbance was read at 550 nm on a Microelisa reader (MR 700, Dynatech Laboratories). For the hydrogen peroxide assay the reaction mixture in each well consisted of HBSS supplemented with 0·56 mM phenol red, 19 U/ml horseradish peroxidase, PMA (40 ng/ml) or oponised zymosan (1 mg/ml), and neutrophils. The microtitre plates were incubated and shaken at 37°C for one hour and terminated with 10 μl of 1N sodium hydroxide. The absorbance was read at 600 nm. Conversion of absorbance to nanomoles of both superoxide and hydrogen peroxide was calculated by a standard method.[32] The results were expressed as nmol of superoxide or hydrogen peroxide/60 minutes/mg of protein.

STATISTICS

All the data were expressed as mean (SEM) except T cell subsets which was expressed as mean (SD). Unpaired Student's *t* test was used for statistical analysis throughout the study except that the Wilcoxon signed rank test was used to analyse the immunoglobulin data. A p value of <0·05 was considered significant.

Results

CLINICAL RESPONSE

All eight patients in group A who received 12 weeks of continuous thymopentin injections completed the clinical trial. Three out of eight patients in group B who received thymopentin injections for the first six weeks and then switched to normal saline injections during the later half of clinical trial, however, dropped out because of flare up of skin lesions to a degree comparable with the period before thymopentin four weeks after stopping thymopentin. No difference in the total severity score was observed between two groups before and during thymopentin treatment, but the total severity score of group B was much higher than that of group A at 12 weeks (p<0·0001, fig 1). In both groups a therapeutic effect became evident after one week of treatment (p<0·03). The results of evaluation by parents matched very well with that of the physician (data not shown).

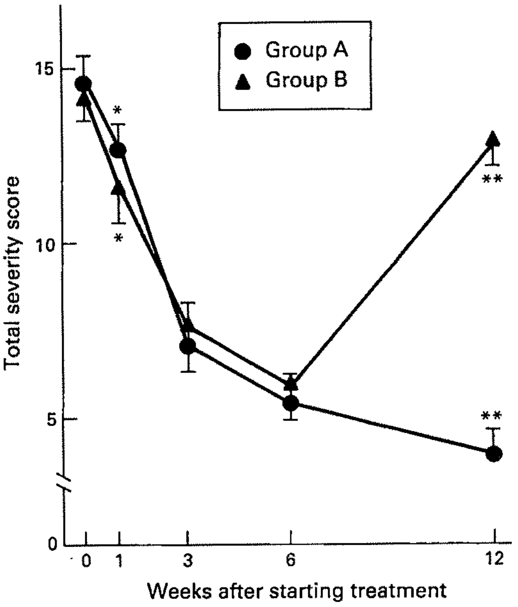

*Figure 1 Total severity score during treatment with 50 mg thymopentin. Group A had 12 weeks continuous treatment with thymopentin and group B had six weeks of thymopentin followed by six weeks of normal saline injections. Vertical bar represents the SEM; *p<0·03, compared with baseline; **p<0·0001, comparison between groups A and B at 12 weeks.*

LABORATORY CHANGES

Figure 2 demonstrates, as an example, that in case 6 the maculopapulovesicles and lichenification over the neck and antecubital areas (left panel) were much improved after three weeks of thymopentin treatment (right panel). In general, erythema and pruritus were the parameters that were improved most quickly and noticeably among the five clinical parameters evaluated, whereas the improvement in scaling/dryness was much less impressive.

Figure 3 shows the in vitro productions of soluble CD4, IL-2R, and cytokines during the course of treatment. the patients produced a greater amount of soluble CD4 (p<0·001), IL-2R (p<0·01), IL-2 (p<0·001), and IL-4 (p<0·001), but less interferon gamma (p<0·01) than normal controls. After treatment, in vitro production of soluble CD4, IL-2R, IL-2, and IL-4 tended to decrease, but only the decrease in IL-2 (p<0·01) and IL-4 (p<0·01) reached a

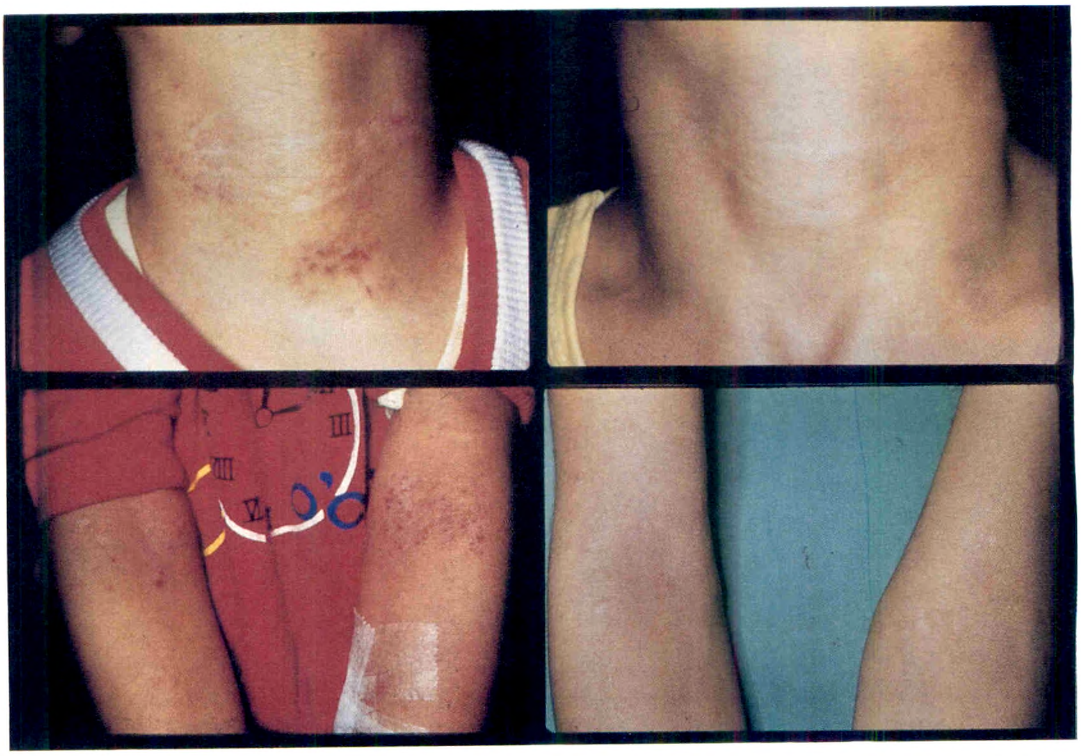

Figure 2 The papulovesicles and lichenification of diseased skin before treatment (left panel) and after three weeks of treatment (right panel).

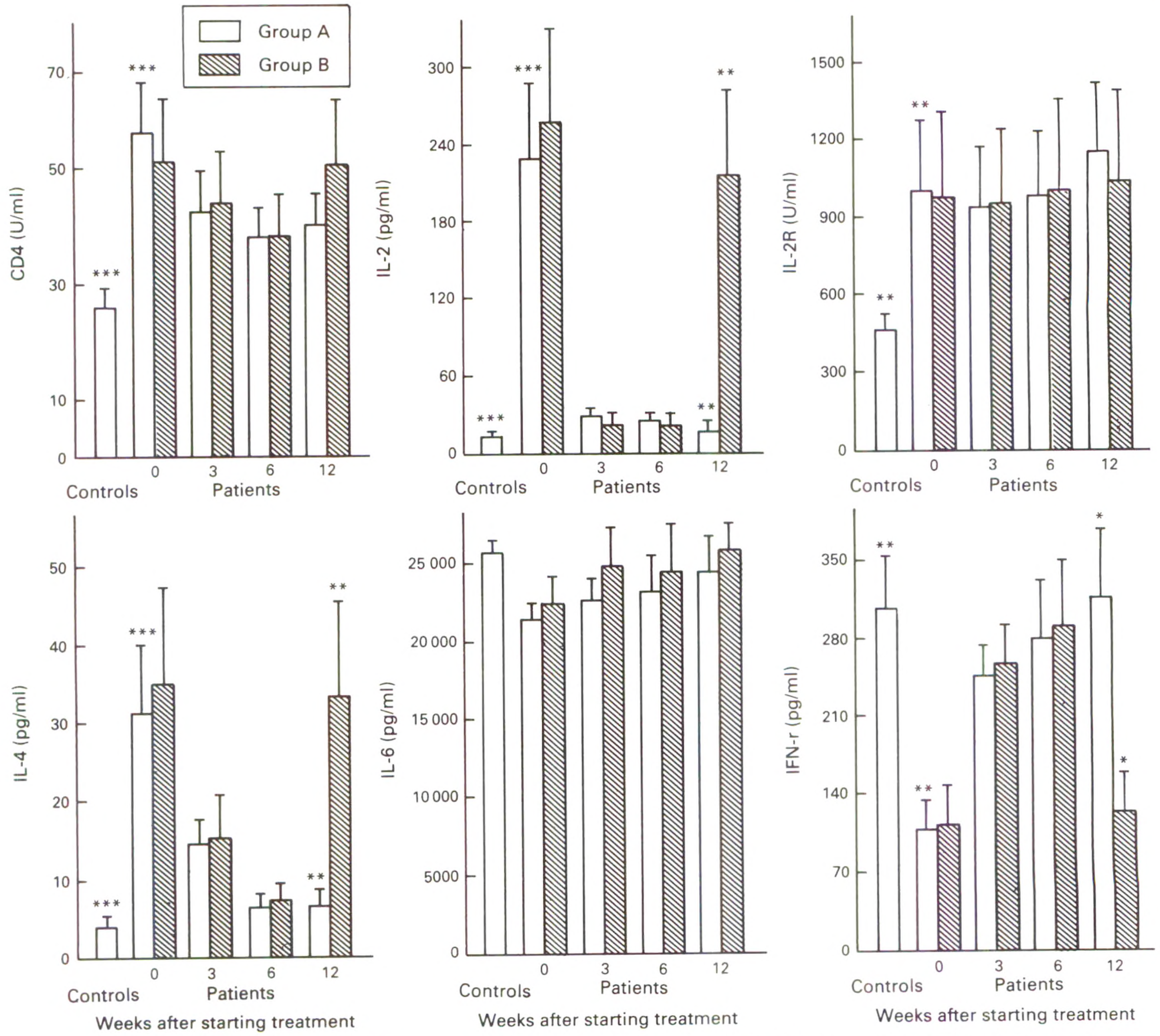

*Figure 3 In vitro productions of soluble CD4, IL-2R, and cytokines during thymopentin treatment. For CD4, ***$p<0·001$; for IL-2, ***$p<0·001$, **$p<0·01$; for IL-2R, **$p<0·01$; for IL-4, ***$p<0·001$, **$p<0·01$; for IFN-r, **$p<0·01$, *$p<0·05$. Data are expressed as mean (SEM).*

significant degree. In vitro production of IFN-r was increased ($p<0{\cdot}05$). No change in IL-6 production was found. Again, those changes were reversed after stopping treatment (group B).

The effect of thymopentin on the distributions of T cell subsets is shown in table 2. When compared with normal controls, the patients with atopic dermatitis had a normal number (%) of total T cells (CD3+), B cells (CD19+), natural killer cells (CD3− CD16+CD56+), suppressor inducer T cells (CD4+CD45RA+), helper inducer T cells (CD4+CD45RA−), cytotoxic T cells (CD8+CD11b−), CD25+, and HLA−DR+ activated CD3 and CD4 cells. However, suppressor T cells (CD8+CD11b+), and CD25+ and HLA−DR+activated suppressor/cytotoxic T cells (CD8+) were appreciably decreased in patients. After thymopentin treatment the suppressor T cells (CD8+ CD11b+) and CD25+ activated CD8+ cells remained very low even at the end of 12 weeks of thymopentin treatment (table 2).

Table 2 Changes of distributions of T cell subsets during thymopentin treatment. Results are mean (SD)%

T cell subset	*Treatment period (n=10)*			*Controls (n=20)*
	0	*3 Weeks*	*6 Weeks*	
CD3+	68·0 (8·7)	66·8 (8·4)	68·3 (6·3)	67·1 (8·2)
CD19+	14·1 (4·8)	17·4 (4·9)	16·6 (7·0)	16·2 (4·9)
CD3−CD16+CD56+	17·3 (9·0)	17·1 (7·5)	16·3 (5·3)	18·3 (9·0)
CD4+	31·9 (8·4)	32·0 (8·1)	33·8 (5·8)	34·8 (6·1)
CD4−CD45RA+	10·7 (3·6)	10·8 (3·9)	11·8 (3·0)	11·9 (3·9)
CD4+CD45RA−	24·7 (5·3)	25·4 (6·8)	24·4 (6·6)	26·7 (7·3)
CD8+	28·5 (5·6)	26·3 (5·9)	29·2 (9·8)	26·7 (9·8)
CD8+CD11b+	5·0 (2·4)*	3·5 (2·1)	5·6 (2·7)	11·9 (3·9)*
CD8+CD11b−	24·2 (5·2)	24·8 (4·8)	26·1 (5·7)	20·0 (9·9)
CD3+CD25+	5·0 (5·1)	4·5 (0·9)	4·1 (1·4)	5·1 (2·8)
CD4+CD25+	5·2 (2·9)	5·6 (2·4)	5·0 (2·3)	6·6 (2·8)
CD8+CD25+	0·7 (1·3)**	0·2 (0·4)	0·2 (0·4)	3·0 (1·9)**
CD3+HLA−DR+	8·2 (5·8)	12·1 (4·4)	15·1 (8·7)	11·3 (4·1)
CD4+HLA−DR+	3·8 (0·9)	6·7 (2·6)	7·4 (2·6)	3·6 (1·3)
CD8+HLA−DR+	4·5 (3·0)***	7·8 (3·5)	8·5 (4·8)	10·3 (4·5)***

$^{*}p=0{\cdot}0001$, $^{**}p<0{\cdot}005$, $^{***}p<0{\cdot}002$.

Table 3 Serum immunoglobulins and in vitro IgE synthesis during thymopentin treatment. Results are mean (SD)

Immunoglobulin	*Treatment period (n=10)*		
	0	*3 Weeks*	*6 Weeks*
IgG (g/l)	10·24 (3·43)*	9·91 (3·32)	8·28 (1·37)
IgA (g/l)	1·52 (0·60)	1·52 (0·56)	1·48 (0·38)
IgM (g/l)	1·49 (0·72)	1·49 (0·74)	1·19 (0·39)
IgE (IU/ml)	3283·2 (1666·7)	2862·1 (1653·2)	3026·8 (1388·8)
In vitro IgE synthesis (pg/ml)	1714·5 (3004·2)	2117·6 (2578·3)	1335·8 (1447·6)

$^{*}p<0{\cdot}05$ (Wilcoxon signed rank test).

The changes of serum immunoglobulin concentrations were followed up serially after thymopentin treatment. IgG and IgM tended to decrease after six weeks of treatment, but not to a significant degree. No change was found for IgA, IgE, and in vitro IgE production throughout the course of trial (table 3).

Figure 4 demonstrates that both plasma histamine and HRF activity were much higher in patients than in normal controls ($p<0{\cdot}001$ for the former and $p<0{\cdot}001$ for the latter). After thymopentin treatment, both plasma histamine and HRF were decreased significantly. The decrease persisted in group A but reversed to pretreatment value in group at the 12th week (A *v* B, $p<0{\cdot}01$).

The respiratory burst activities of polymorphonuclear leucocytes after stimulation with PMA are shown in fig 5. The production of superoxide ($p<0{\cdot}001$) and hydrogen peroxide ($p<0{\cdot}001$) before thymopentin treatment was much higher than normal controls and the

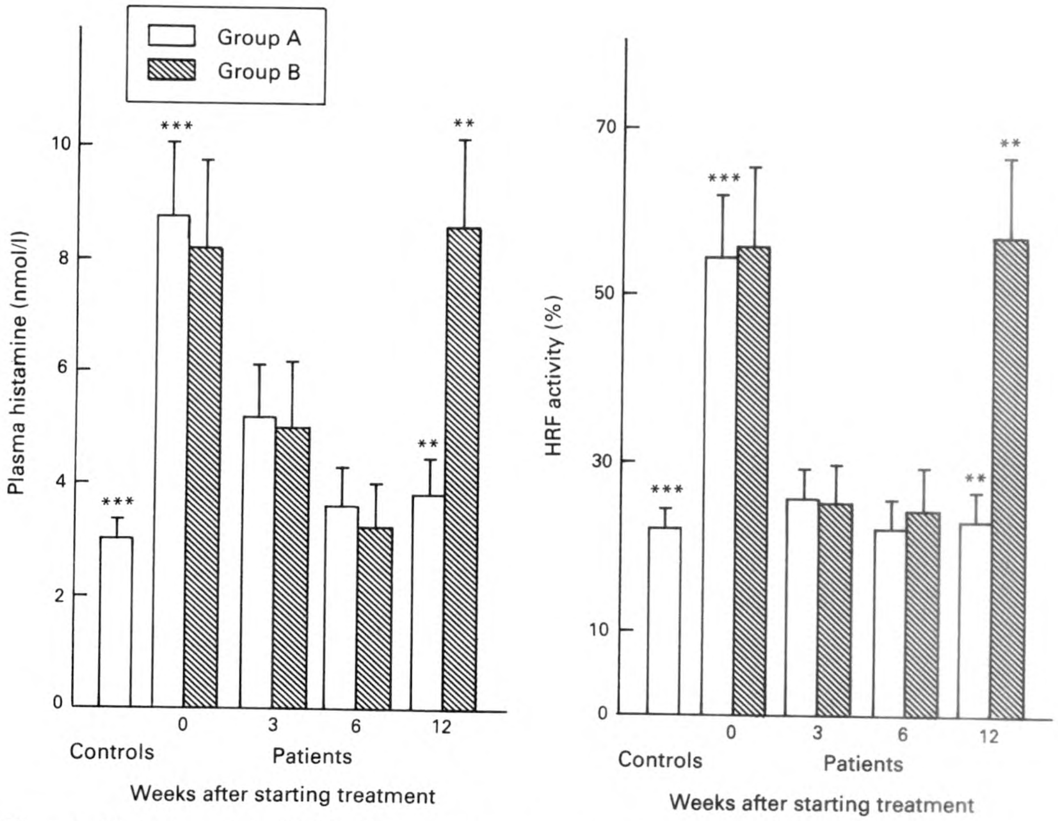

Figure 4 Plasma histamine and HRF activity during thymopentin treatment. For plasma histamine, $^{***}p<0{\cdot}001$, $^{**}p<0{\cdot}01$; for HRF activity, $^{***}p<0{\cdot}01$, $^{**}p<0{\cdot}01$. Data are expressed as mean (SEM).

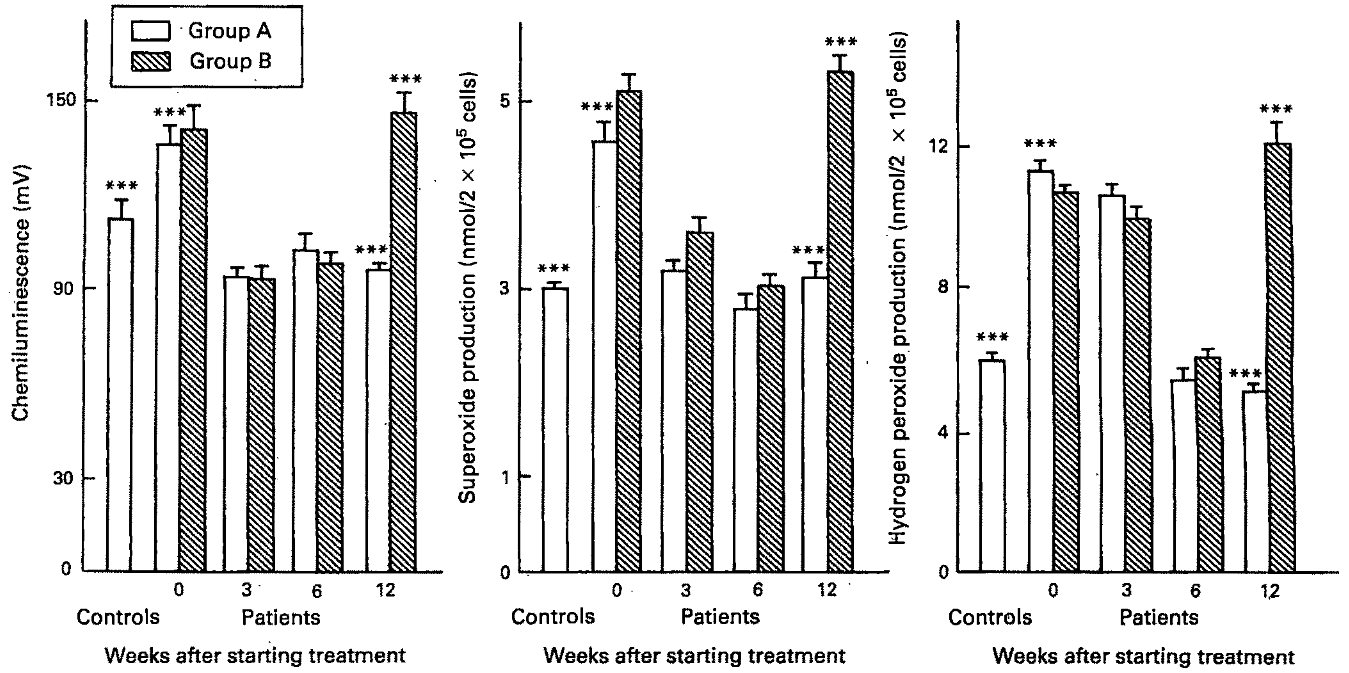

*Figure 5 Respiratory burst activities of polymorphonuclear leucocytes stimulated by PMA. For chemiluminescence, ***$p<0{\cdot}001$, ***$p<0{\cdot}001$; for superoxide production, ***$p<0{\cdot}001$, ***$p<0{\cdot}001$; for hydrogen peroxide production, ***$p<0{\cdot}001$, ***$p<0{\cdot}001$. Data are expressed as mean (SEM).*

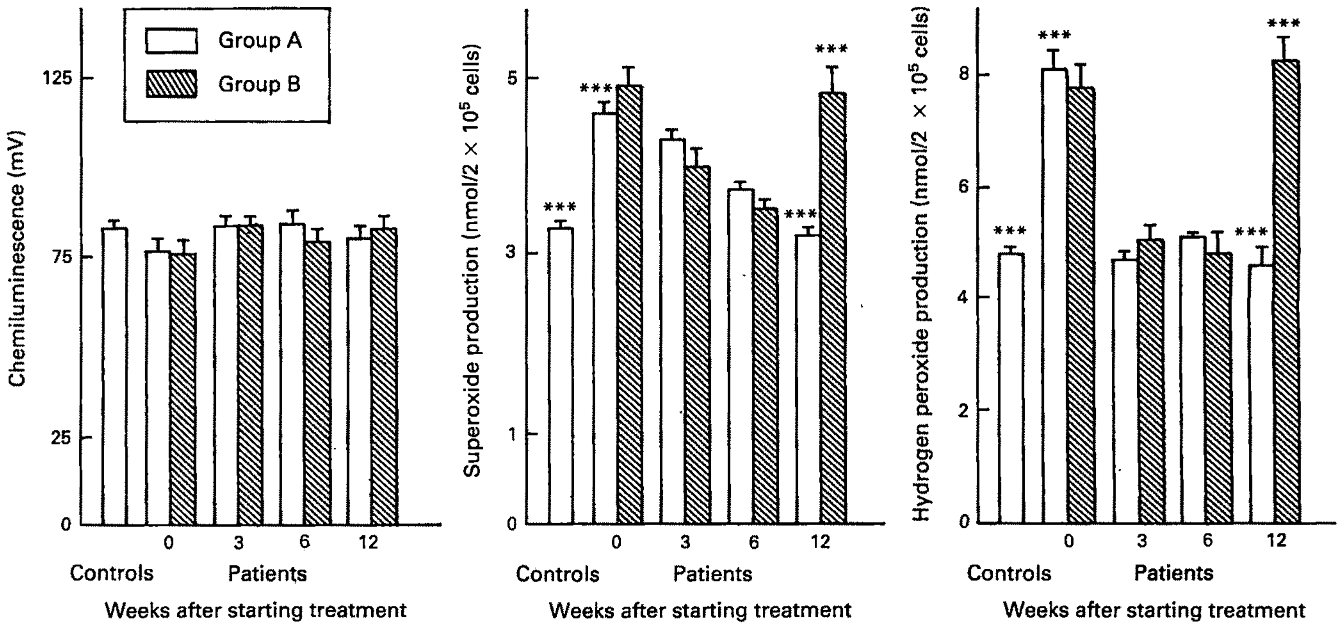

*Figure 6 Respiratory burst activities of polymorphonuclear leucocytes stimulated by serum opsonised zymosan. For superoxide production, ***$p<0{\cdot}001$, ***$p<0{\cdot}001$; for hydrogen peroxide production, ***$p<0{\cdot}001$, ***$p<0{\cdot}01$. Data are expressed as mean (SEM).*

heightened activity decreased to normal after treatment. A similar tendency was found when polymorphonuclear leucocytes were stimulated with opsonised zymosan (fig 6); their enhanced activation returned after discontinuation of thymopentin (group B).

Discussion

All patients responded to thymopentin treatment. The itching, scratching, and erythema decreased appreciably three weeks after treatment (fig 1), and the improved skin texture due to subsidence of papulovesicles and lichenification usually occurred later (fig 2). The improvement continued in those patients (group A) who received thymopentin treatment throughout the 12 week period, however, the eczema flared up in all patients of group B four weeks after discontinuation of thymopentin (fig 1). The use of topical steroids and antihistamines could be reduced and no serious side effects were observed except transient pain at the injection site. The beneficial clinical response was largely similar to that reported by Kang *et al*[22] and Leung *et al.*[23]

The immunological mechanism(s) responsible for the clinical efficacy of thymopentin has not been well studied. Cooper *et al* reported that thymopentin could influence the in vivo and in vitro production by atopic dermatitis MNCs.[21] The same group further described increased CD8+ (suppressor/cytotoxic) cells after six weeks of thymopentin administration.[22] The results obtained in our study could not confirm their hypothesis: (i) total serum IgE and in vitro IgE production were not changed after treatment, and (ii) the CD8+CD11b+ suppressor T cells, but not the total number of CD8+ suppressor/cytotoxic T cells, were decreased in patients with atopic dermatitis, and thymopentin treatment failed to increase the CD8+CD11b+ suppressor and CD8+CD25+ activated T cells. Recent studies have demonstrated that peripheral blood MNCs from patients with atopic dermatitis produced increased concentrations of IL-4,[33] a cytokine that induces IgE synthesis,[34–36] and decreased concentrations of interferon gamma[37] a cytokine that inhibits IL-4 dependent IgE synthesis.[34–36] Our results confirm those reports,[33 37] and furthermore this study showed that thymopentin treatment tended to suppress the production of IL-4 and enhanced the production of interferon gamma in vitro. However, Li *et al* recently reported that the total serum IgE and specific IgE antibodies were not decreased in patients with allergic rhinitis after receiving interferon gamma treatment in both periods of off season and during season.[38] Vercelli *et al* also found that anti-IL-4 and interferon gamma were unable to suppress the in vitro spontaneous IgE synthesis in patients with hyper-IgE syndrome,[39] and no significant difference in mitogen induced productions of IL-4 and interferon gamma was detected between HIE patients and normal controls. Thus, mechanisms other than antigen-IgE immune reaction may account for the rather quick appearance of clinical benefit of short term thymopentin administration in the treatment of atopic dermatitis.

It is important to note that HRF and plasma histamine concentrations were decreased after thymopentin treatment (fig 4). Furthermore, the augmented activation of polymorphonuclear leucocytes was also suppressed, as evidenced by the lessened respiratory burst activities (fig 5 and 6). Sampson *et al* recently reported that patients with atopic dermatitis caused by food allergy produced significantly less HRF after the offending food allergen was eliminated from the diet for an extended period.[40] Our recent study also demonstrated decreased production of and responsiveness to HRF in asthmatic patients benefited by successful immunotherapy.[27] Thus, the decreased production of HRF and decreased release of polymorphonuclear leucocytes derived inflammatory mediators may account partly for the clinical efficacy of thymopentin treatment in patients with atopic dermatitis.

One of the shortcomings of this paper is lack of immunohistological studies of diseased skin before and after thymopentin treatment. Such studies would provide the most direct information that could be used to explain the clinical efficacy of thymopentin. Unfortunately, we are unable to obtain consents from parents to do skin biopsies.

Finally as no serious side effects are encountered during the 12 week period of treatment and there is still no satisfactory management for severe atopic dermatitis, thymopentin may be used in those patients with atopic dermatitis who are refractory to traditional treatment. Studies with longer duration and larger number of patients are needed before the rationale for such kind of treatment can be justified.

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Maths and mumps

Given two different vaccines for the same disease, one more effective but with a higher complication rate than the other, which is it best to use? This problem is posed by the existence of two mumps vaccines, the Urabe Am 9 and the Jeryl Lynn strains. The former has an estimated protective efficacy of about 98% and the latter about 94% whereas the estimated complication rates are one in between 62 and 400 thousand for the Urabe Am 9 strain and one in between 250 and 1800 thousand for the Jeryl Lynn strain. D J Nokes and R M Anderson (*Lancet* 1991;**338**:1309–12) have applied a mathematical model to the available data in order to calculate the number of complications, from either the natural disease or the vaccine, to be expected over a period of 20 years after the introduction of a vaccination programme with either of the two vaccines. Incorporated within their calculations is an estimate of the degree of persistence of the natural disease at various levels of vaccine uptake within the population. Thus at 70% uptake the natural disease is still prevalent whereas at over 80% uptake the natural transmission of infection virtually ceases. Their model predicts that at the lower level of vaccine uptake (70%) the vaccine strain with greater efficacy and higher complication rate (Urabe Am 9) is associated with fewer complications overall as most of the complications at this level of vaccination are produced by the natural disease. On the other hand, at 80 to 90% uptake most of the complications are caused by the vaccine as the natural disease becomes uncommon, and the safer vaccine (Jeryl Lynn) is to be preferred.

So the answer is, if you can guarantee a high acceptance of the vaccine in your population use the safer vaccine, but if you can't, use the more effective one.

If you can achieve high immunisation rates you automatically create an interesting problem in ethics. The natural disease is now rare and most complications arise from the vaccine. So why not cheat? Why not encourage everybody else to have their babies immunised but leave yours alone? It would have to be secret, of course, because, if everybody else tumbled to the same ruse your baby would finish up at high risk of the disease again. Why should we be concerned about the welfare of others? You may have a theology based explanation but non-theological ethicists seem to debate the matter endlessly without coming to any satisfactory conclusion.[1]

ARCHIVIST

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Policies for control of communicable disease in day care centres

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Abstract

A survey was carried out to identify the availability and quality of guidelines for the prevention and control of communicable disease and procedures in use in child day care centres within the South West Thames Regional Health Authority.

A sample of 50 day care centres was investigated including those funded by social services and privately funded day care centres. Policies for the prevention and control of communicable disease for children and staff showed a wide variation between different centres. Exclusion criteria were unclear especially in relation to carriers of the hepatitis B virus and HIV positive children. Channels for reporting and seeking advice were inconsistent. It is recommended that clear and up to date written guidelines on the prevention and control of communicable diseases should be available in all day care centres with clear indications of good practice and channels for reporting and advice. It is desirable that guidelines are agreed by the different health and local authorities throughout the region.

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The number of child day care centres in the United Kingdom has been growing steadily and is expected to increase further in the future.[1 2] Care is provided on a regular paid basis for children under the age of 5 years in various settings outside the child's home such as nurseries, play groups, or nursery schools which are registered with local authority social services departments. Growth has been particularly great in the private sector, increasing from 1093 nurseries (28 972 places) in 1986 to 1781 nurseries (46 938 places) in 1989.

Children attending day care centres have been shown to be at increased risk of infection, in particular from diarrhoeal conditions, otitis media, varicella, hepatitis A and invasive *Haemophilus influenzae* type b disease.[3-6] In addition there is a potential for transmission to parents and care providers of other infections such as rubella and cytomegalovirus,[7] with possible risks for the fetus in susceptible pregnant contacts. Concern has arisen about the possibility of spread of two blood borne organisms in the child day care setting: hepatitis B virus and HIV.[8-10]

Day care provides a much needed service for children and families of whom a significant proportion is at high risk of health problems.[11] It is important that staff know how to minimise health hazards for the children in their care and for themselves. In the past year an outbreak of shigellosis and of cryptosporidiosis occurred in nurseries in the South West Thames region which has a population of approximately 170 000 children aged under 5 years. On investigation a general lack of knowledge of procedures for the prevention and control of communicable diseases was found. The study reported here was undertaken to assess the availability and quality of information in the form of policy or guidelines, or both, in day care centres in the region and their use.

Methods

A sample of 50 day care centres was taken from those registered with each of the eight local authorities in the region. Drop in centres, parent-toddler groups, nursery schools, and childminders were excluded. All 20 centres funded by the social services and a random sample of the 352 privately run centres were included with representative numbers from each local authority.

Information was obtained by a questionnaire sent to the director of each day care centre and included: numbers of children attending and their sociodemographic characteristics; any requirement for immunisation before entry; whether the centre gave advice or more actively promoted immunisation, or both; from where advice about infectious diseases was obtained; episodes and reporting of infections over the previous year; policies for excluding children because of communicable disease; hygiene and food preparation practices; and pre-employment health screening of staff.

All the local authorities, each of the 13 district health authorities in the region, and each day care centre selected for study were asked if they used any written guidelines about communicable disease control and to forward copies.

Interviews were carried out with directors of three day care centres to validate and explore in depth the findings of the questionnaire survey.

Results

Completed questionnaires were received from 37 day care centres, an overall response rate of 74%. Fifteen questionnaires were returned by the 20 sampled day care centres funded by social services and 22 by the 30 private centres.

The number of children (1324) attending the 37 centres sampled represented 66% of the total 927 places in social services and 9% of those (total 7927 places) in privately run day care centres in the region. Ninety four per cent of the children were aged 2 years or over, 5% (62 children) were aged between 1 and 2 years, and 12 children were aged less than 1 year.

Most day care centres (73%) had places for between 20 and 40 children; 18% of centres catered for less than 20 children, and nearly 9% for more than 40.

Day care centres funded by social services gave priority to children with 'special needs'. Overall 15% of children were categorised in this way with about two thirds of these reported to have 'social' needs, including ill, single, or unsupported parents, or risk of abuse. Other children had learning difficulties, language delay, developmental and behavioural problems, physical impairments such as cerebral palsy, or sensory deficit, but only children with mild mental handicap were said to be accepted. Only three children with special needs were attending the privately run day care centres.

GUIDELINES

Guidelines specifically for communicable disease control were available to day care centres from six of the eight social services departments but were not provided routinely to privately funded centres. These different social services guidelines had been produced between 1984 and 1991 and often gave incomplete or out of date information. One set of guidelines related only to HIV infection; others lacked information about good practice with regard to immunisation, exclusion criteria for children with infection, or gave no indication about how or when to report infectious disease. All the guidelines provided a telephone number for making inquiries which was invariably that of the local environmental health department but was not always correct. A set of guidelines had recently been drawn up by two district health authorities with the collaboration of consultants in communicable disease control, community paediatricians, and the local authorites. These were comprehensive and up to date and included signs and symptoms for the most common infectious diseases, criteria for reporting and exclusion, and information about HIV and hepatitis B, recommended immunisations, general hygiene, and first aid. The necessary measures for protection for staff from rubella and screening for tuberculosis were outlined.

Table 1 Policies for communicable disease prevention and control in day care centres

Policy	*Day care centres*	
	Social services (n=15)	*Private (n=22)*
Had written policy for infection control	13	17
Had written hygiene policy	14	18
Recorded medical history of children	15	19
Recorded past infectious disease in children	14	16
Recorded immunisation history of children	15	19
Recommended parents to update immunisation	13	13
Arranged for immunisation	7	1
Gave immunisation on site	7	3
Had written guidelines on exclusion criteria	8	7
Would exclude children carrying the hepatitis B virus	4	6
Would exclude HIV positive children	1	4

Table 2 Pre-employment staff screening policies for communicable disease prevention and control in day care centres

Policy	*Day care centres*	
	Social services (n=15)	*Private (n=22)*
Used pre-employment questionnaire	15	13
Tuberculin skin testing	8	6
Recommended rubella immunisation (female staff)	5	6

Table 1 summarises the content of policies reported to be used within the day care centres. Hygiene policies were used in nearly all social services centres. Their own guidelines for hygiene had been produced by 10 of the private centres but three said they used 'common sense'. Children's immunisation status was not recorded routinely nor recommendations made for those children found not to be fully protected. Almost half the social services but few private centres arranged to take children to be immunised or provided immunisation on site. Criteria for the exclusion of children varied and 22 of the centres did not have written guildelines for these. It was clear that in many instances parents were offered conflicting advice from day care centres and general practitioners. Five centres said they would not accept a child who was HIV positive, though none had actually been faced with the problem. Several private centres were not sure what they would do in such an instance nor where to ask for expert advice. Nearly a third of the centres reported that children known to be carrying the hepatitis B virus would be excluded and one centre, having excluded a child for this reason, asked for further advice on the study questionnaire form.

Table 2 summarises the policies for staff health. Pre-employment questionnaires were used in all social services day care centres and in over half of those in the private sector. Pre-employment tuberculin skin testing was carried out in less than half of the centres. A third of the centres made recommendations to their female staff about rubella immunisation but there were no specific recommendations for pregnant staff unless a case of rubella occurred at a centre. One centre offered hepatitis B immunisation to all its staff.

Table 3 summarises how the day care centres reported infectious disease and sought advice. These procedures were found to be extremely irregular. Three quarters of the centres had no set pattern for seeking advice but used a variety of sources of help. Private centres usually contacted a general practitioner or health visitor, or both, for advice. Social services centres also contacted a health visitor but were more likely to contact an environmental health officer, a community paediatrician, or consultant in communicable disease control. There was felt to be no clear need to report an occurrence if a disease was not on the list of notifiable diseases, as for diarrhoea, and there was general uncertainly about the circumstances in which reporting is advisable.

Table 4 shows the infections reported to have occurred during the previous year. Chickenpox, diarrhoea, and ear infections were common, with

Table 3 Advice and reporting for communicable disease in day care centres

Health 'consultant'	*From whom advice usually requested**		*To whom infections usually reported*	
	Social services (n=15)	*Private (n=22)*	*Social services (n=15)*	*Private (n=22)*
Health visitor	7	12	1	0
General practitioner	2	10	1	0
Community paediatrician	3	0	1	0
Consultant in communicable disease control	5	2	3	0
Local authority				
Social services	7	9	4	4
Environmental health officer	12	4	0	0
Unspecified	0	0	7	3
District health authority	0	0	4	4

*Several advisors may be contacted by each centre.

Table 4 Infections reported by day care centres (DCCs) during 1990–1

Type of infection	*No of DCCs reporting episodes or cases (n=37)*	*No of DCCs specifying number affected*	*Estimated No affected*	
			Children	*Staff*
Measles	14	9	15	0
Mumps	7	6	15	4
Rubella	7	6	9	1
Whooping cough	3	3	3	0
Meningitis	2	2	2	0
Chickenpox	33	27	258	6
Diarrhoea	26	16	85	30
Dysentery (shigella)	1	1	13	1
Cryptosporidiosis	1	1	6	0
Food poisoning	2	1	2	2
Ear infections	23	17	78	4
Skin infections	6	4	9	2
Glandular fever	3	1	11	3
Hand/foot/mouth diseases	2	2	12	0

one outbreak each of shigella and cryptosporidiosis. Vaccine preventable diseases were reported in most centres but mostly as isolated cases.

Discussion

This investigation showed a lack of clear policies regarding communicable disease prevention and control in day care centres in the South West Thames Regional Health Authority. Although guidelines had been prepared in many instances their availability and use varied as did systems of reporting between centres and districts.

Information about the epidemiology and control of communicable disease in day care centres is incomplete. Outbreaks of a number of diseases have been documented, however.[12–16] An outbreak of cryptosporidiosis was reported in a nursery in the region in 1990 (E Rang, personal communication). Other studies have reported an incidence rate of diarrhoeal diseases two to three times greater in children attending day care centres than in those staying at home,[4 17] particularly diarrhoea caused by giardia and cryptosporidium.[18–20] Epidemics of subclinical verocytotoxin producing *Escherichia coli* associated with haemolytic uraemic syndrome have also been reported,[16] in addition to hepatitis A outbreaks characterised by clusters of clinical hepatitis among staff and parents of children in the day care centres.[13 21]

In our survey most of the centres reported episodes of infectious disease in attenders and staff but it is not possible to make epidemiological inferences from these data because the reported cases were not validated and because no data are available about disease incidence in children not attending day care centres. The risk of a particular infectious agent being introduced depends on its prevalence in the community and the number of susceptible subjects in the centre. Once introduced transmission depends partly on the agent, as in mode of spread, infective dose, survival in the environment, and frequency of unrecognised asymptomatic infection, and also on characteristics of the centre such as ages of the children and hygienic aspects of child handling.

The risk of primary *H influenzae* type b infection has been shown in other studies to be significantly increased in day care attenders,[14] with an even greater risk in children younger than 2 years and during the first month of attendance.[3] *H influenzae* type b vaccine for children aged two years of age will be introduced in the United Kingdom in late 1992 and this will hopefully reduce the incidence of infections such as otitis media in this age group.

Day care centres are an increasingly important public health setting which could provide opportunities for positive contributions to child health such as ensuring adequate immunisation of children before school age. There was evidence in our study that not all day care centres recommended that parents update their children's immunisation, though nearly half the day care centres funded by social services did arrange for immunisation on site. Any guidelines should emphasise the need to ensure up to date immunisation. Children who have not completed a primary course are likely to be exposed to vaccine preventable diseases on entering day care and also to place their younger siblings who have not been immunised at risk. The national immunisation schedule introduced in May 1990 offers protection to babies from a much younger age (2, 3, and 4 months), and parents of children in day care facilities could be targeted to encourage immunisation uptake not only of children attending but of children in the household.

There is a need to address concerns about the transmission of blood borne infections such as hepatitis B and HIV as the study showed that a disturbingly high number of day care centres would exclude a child known to be carrying the hepatitis B virus. Child care providers should be educated about the modes of transmission of blood borne diseases and their prevention.[10 22–24]

Studies in day care centres have shown that young children may shed cytomegalovirus for a number of years after infection and may transmit the virus to other children in the centre and to their mothers and child care providers with whom they are in close contact.[7 25–31] The incidence of congenital cytomegalovirus infection is three per 1000 live births in the United Kingdom.[32] Ninety per cent of these children are asymptomatic and in most there are no adverse effects. In the United Kingdom, by the age of 12 months, 20% of children have acquired cytomegalovirus infection and because most of these will not be recognised excretors it is advisable that all women caring for young children wash their hands carefully after contact with body secretions, especially urine and saliva, to minimise the chance of infection.[33] Guidelines for day care centres should emphasise the necessity for good personal hygiene to reduce readily transmitted infections such as cytomegalovirus.

Pre-employment screening for tuberculosis was carried out in fewer than half of the day care centres studied and rubella immunisation of female staff recommended in less than one third. Pre-employment screening of staff in day care centres for tuberculosis by the Heaf test has been recommended[34] and should be included in policies along with guidance to women of childbearing age about the necessity to ensure their own rubella immunity.

This study found a great diversity in the people who day care centres contact over infectious disease matters. There is a need to clarify the appropriate sources of information and the circumstances in which to report communicable diseases.

Recommendations

(1) Guidelines about the prevention and control of communicable disease should be made available to and should be used by all social services and privately funded day care centres. Good practice with regard to communicable disease control could be a requirement for registration of day care centres by local authorities.

(2) Guidelines should be produced and agreed by consultants in communicable disease control, district immunisation coordinators, community paediatricians, family health service authorities, local authorities, and community nursing staff. It is desirable that the same guidelines are used in a number of contiguous health and local authorities.

(3) Guidelines should include recommendations based on the most up to date knowledge of good practice in personal hygiene, food preparation, immunisation, exclusion criteria for children with communicable disease, and staff health and screening policies.

(4) A clear and efficient method of reporting and seeking expert advice about communicable diseases should be established and agreed by the day care centres, consultants in communicable disease control, and local authorities.

(5) The guidelines should be disseminated widely and updated regularly.

We thank the day care centres and local authority social services departments for their help with this study and Dr David Elliman for his valuable advice.

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Endocrine deficit after fractionated total body irradiation

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Abstract

Endocrine function was assessed in 31 children (17 boys) after fractionated total body irradiation used in the preparative regimen for bone marrow transplantation. Endocrine dysfunction was present in 25 children. Fifteen of 29 had growth hormone insufficiency 0·9–4·9 years after total body irradiation, yet only three of the 15 had received previous cranial irradiation. Five of 30 had thyroid dysfunction: two with a low thyroxine and raised thyroid stimulating hormone (TSH) concentration and three with a raised TSH and normal thyroxine concentration. Thus the incidence of thyroid dysfunction (16%) is much lower than that reported after single fraction total body irradiation (39–59%). In only two children were abnormalities of the hypothalamic-pituitary-adrenal axis demonstrated. The majority of pubertal children assessed (n=15) showed evidence of gonadal damage. All the pubertal girls (n=5) had ovarian failure, although there was evidence of recovery of ovarian function in one girl. All seven boys in late puberty showed evidence of damage to the germinal epithelium, and two of three in early puberty had raised follicle stimulating hormone concentrations. Despite the use of a fractionated total body irradiation regimen, endocrine morbidity is substantial and children undergoing such procedures will require long term endocrine review and management.

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Bone marrow transplantation (BMT) is now an established treatment for refractory malignant disease such as acute lymphoblastic leukaemia, either in first remission or after a relapse, and acute myeloblastic leukaemia in first remission. Since the 1960s, when BMT was almost universally unsuccessful, advances in histocompatibility testing and improvements in supportive care have led to increasing numbers of young adults surviving childhood malignancy. Five year survival rates have increased dramatically from 2% to 47% in acute lymphoblastic leukaemia and 2% to 21% in acute myeloblastic leukaemia between the decades 1954–63 and 1974–83.[1]

To date most of the work on the endocrine consequences of BMT have been described in an adult population in whom particularly high incidences of gonadal and thyroid dysfunction have been reported.[2] There is little information on the outcome in children. In the only sizable surveys, single fraction total body irradiation was used in the preparative regimen,[3] or a population was described in whom either single fraction or fractionated total body irradiation was employed.[4] It is not clear in the latter study if the prevalence of endocrine complications differ after the two irradiation schedules.[4] Both studies report a high incidence of growth hormone deficiency, hypogonadism, and thyroid dysfunction.[3 4]

We have studied the endocrine morbidity after BMT in children from two major UK centres at which the total body irradiation is delivered in multiple fractions rather than a single dose, to assess whether this has a less detrimental endocrine outcome.

Patients and methods

Thirty one children (17 boys) who received total body irradiation before BMT between 1978 and 1990 at the Royal Hospital for Sick Children, Glasgow, and the Christie Hospital, Manchester were studied. All were in complete remission at the time of endocrine assessment, which was performed between 0·5 and 7·8 years after total body irradiation. The mean age at transplantation was 8·1 (range 2·2–15·2) years. The primary diagnosis was acute lymphoblastic leukaemia (n=11), acute myeloid leukaemia (n=15), chronic granulocytic leukaemia (n=3), and neuroblastoma (n=2).

Seventeen children underwent allogenic and 14 autologous BMT. The conditioning chemotherapy consisted of cyclophosphamide 60 mg/kg/day on two consecutive days (in 29 children), or melphalan 140 mg/m^2 as a single dose (in the two children with neuroblastoma).

All 31 children received fractionated whole body irradiation, delivered by a 4 MV linear accelerator at a dose rate of 10 cGY/minute. The median dose was 1200 (range 1100–1520) cGy in 6 (3–8) fractions, over 3·5 (2–5) days.

In the treatment of the original disease, all children had received multiagent cytotoxic chemotherapy for varying lengths of time. Children with acute lymphoblastic leukaemia were treated with established Medical Research Council (MRC) protocols. Patients with acute myeloid leukaemia were treated with either the MRC acute myeloid lymphoma protocols or the Bristol Myers protocol. All patients with acute lymphoblastic leukaemia or acute myeloid leukaemia received intrathecal methotrexate, and/or cytosine arabinoside. Patients with chronic granulocytic leukaemia were treated with hydroxyurea with or without busulfan. The patients with neuroblastoma received six courses of OPEC chemotherapy (vincristine, cis-platinum, etoposide, and cyclophosphamide).

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Twenty seven children were transplanted in first remission and four in second remission. Seven children had received radiotherapy before total body irradiation. Four children received cranial irradiation at a dose of 1800–2400 cGy at a median time of 3·7 (range 3·2–3·8) years before total body irradiation. Two of these four also received testicular irradiation at a dose of 1000 and 600 cGy in six and three fractions respectively over three days. One child received mediastinal irradiation, one orbital irradiation, and one received splenic irradiation.

Only one child developed graft-versus-host disease, which was treated with prednisolone for seven weeks. No child was taking immunosuppressive treatment at the time of endocrine assessment.

In all 31 patients basal concentrations of gonadotrophins (follicle stimulating hormone (FSH) and luteinising hormone), oestradiol or testosterone, thyroxine, and thyroid stimulating hormone (TSH) were measured. In 19 children a basal measurement of prolactin was made.

Twenty nine patients underwent full combined dynamic tests of hypothalamic-pituitary function performed in the fasting state between 0·5 and 7·8 years after BMT. Growth hormone secretion and the pituitary-adrenal axis were assessed by an insulin tolerance test (0·2 U/kg human soluble insulin). The gonadotrophin response to an intravenous bolus of gonadotrophin releasing hormone (GnRH) (100 μg/m^2, to a maximum of 100 μg) and TSH response to an intravenous bolus (3 μg/kg to a maximum of 200 μg) of thyrotrophin releasing hormone (TRH) were also assessed.

Pubertal status was assessed clinically by the method of Tanner.[5] Testicular volumes were estimated by comparison with the Prader orchidometer.[6] None of the patients was taking corticosteroids or thyroxine at the time of dynamic testing. Sex steroid replacement therapy was discontinued four weeks before endocrine assessment because of the potential effect of exogenous oestrogen on cortisol binding and thyroxine binding globulins.

All hormone measurements were performed using standard radioimmunoassays.

Results

Twenty five of 31 children had abnormal endocrine function.

GROWTH HORMONE

Fifteen of 29 (52%) children had growth hormone insufficiency as defined by a growth hormone response of less than 10 μg/l (20 mU/l) to an insulin tolerance test, performed a mean time of 2·4 (range 0·5–7·4) years from total body irradiation. Three of the 15 had received previous cranial irradiation. One child, who had received cranial irradiation in addition to total body irradiation, had normal growth hormone secretion to provocative testing. Nine children are now receiving growth hormone treatment.

THYROID FUNCTION

Thyroid function was assessed between 0·6 and 7·8 (mean (SD) 3·2 (1·8)) years after total body irradiation. Five of 30 children showed evidence of thyroid dysfunction. Two had primary hypothyroidism (thyroxine <50 nmol/l, TSH >6 mU/l) and three compensated thyroid dysfunction (normal thyroxine, TSH concentration >6 mU/l), two of whom showed an exaggerated peak TSH response to TRH. (Normal peak TSH response to TRH between 5–32 mU/l.[7]) All five are receiving thyroxine.

ADRENAL FUNCTION

Two children had biochemical evidence of an abnormality of the pituitary-adrenal axis with a very low basal cortisol concentration in both (50 and 60 nmol/l respectively) and a borderline low peak cortisol response to insulin hypoglycaemia of 413 nmol/l in one child (normal >500 nmol/l).

GONADAL FUNCTION

Gonadal function was studied in all 31 children.

All five girls who were pubertal at the time of gonadal assessment had ovarian failure with raised basal gonadotrophins, exaggerated gonadotrophin responses to GnRH, and low oestradiol concentrations. All five have required sex steroid therapy to induce or maintain progress in puberty, to avoid symptoms of oestrogen deficiency, and to reduce the risks of osteoporosis. One girl, pubertal at the time of total body irradiation, developed ovarian failure after the procedure but has since shown evidence of recovery of ovarian function two years after the total body irradiation. Although the adequacy of ovarian function could not be assessed comprehensively in the children who were prepubertal at the time of the study, the older girls of peripubertal age showed evidence of ovarian damage with raised basal gonadotrophins and low oestradiol concentrations.

All seven boys in late puberty at the time of endocrine assessment had a raised basal FSH concentration indicative of damage to the germinal epithelium, and in six of the seven the testicular volumes were small for pubertal stage. One had had previous testicular irradiation. Two of the three boys in early puberty had a raised FSH concentration but no firm conclusions could be drawn about their testicular size at this pubertal stage (G2, PH2). One of the three had received previous testicular irradiation.

No boy had overt Leydig cell failure. Those boys in late puberty had normal testosterone concentrations, although four of seven had raised basal luteinising hormone concentrations. One of the three boys in early puberty had a raised luteinising hormone. Seven boys were still prepubertal at the time of the study and therefore the adequacy of testicular function could not be assessed. However although all had normal testosterone and luteinising hormone concentrations, the FSH was raised in three of the seven boys.

PROLACTIN

Only one of 19 children (5%) had a prolactin concentration (422 mU/l) above the normal range of 350 mU/l.

Discussion

The radiobiological effect of irradiation on normal tissues is related not only to the total dose of radiation delivered, but also to the dose per fraction and is inversely related to the overall treatment time.[8 9] It would be anticipated therefore that fractionated total body irradiation would cause less endocrine deficit than single fraction total body irradiation. None the less, in this study which includes only patients receiving fractionated total body irradiation we have shown that endocrine morbidity is considerable. Confounding variables were restricted to a minimum in that only four of the 31 children had received previous cranial irradiation, only one child had experienced a previous episode of graft-versus-host disease, and no child was currently on steroids or chemotherapy.

Despite a total total body irradiation dose of only 1100–1520 cGy to the hypothalamic-pituitary axis, 52% (15/29) of children were growth hormone insufficient after total body irradiation (mean interval 2·4 years), yet only three of these had previous cranial irradiation. Sanders *et al* described a similar incidence of growth hormone insufficiency in children one to 13 years after receiving total body irradiation as a single dose (920–1000 cGy) or fractionated regimens of 1200–1575 cGy over 6–7 days but did not distinguish between the impact of these two schedules.[4 10] It is likely that the prevalence of growth hormone insuffiency will increase with time from total body irradiation[11 12] and thus long term studies will be required to appreciate the full impact of fractionated total body irradiation on growth hormone secretion. Adults receiving similar doses of fractionated total body irradiation, however, do not develop growth hormone insufficiency when assessed at a similar time from irradiation,[2] suggesting that growth hormone secretion in the prepubertal and early pubertal child is more vulnerable to the effects of hypothalamic-pituitary irradiation than in the adult.

In this study we have concentrated only on endocrine deficit after total body irradiation and not the effect of fractionated total body irradiation on growth. Little is known about the effect of fractionated total body irradiation on cartilage growth and the resultant effect on body proportions in those with normal and subnormal growth hormone secretion. More longitudinal data were required before these effects can be meaningfully assessed.

The incidence of thyroid dysfunction (16%) after fractionated total body irradiation is much lower than that reported after single fraction total body irradiation (39–59%).[3 4] The incidence of thyroid dysfunction may vary with time in that recovery of thyroid function has been observed in patients with documented thyroid dysfuction after total body irradiation.[13] Radiation appears to be the major, if not sole cause of subsequent thyroid dysfunction as BMT without irradiation is not associated with thyroid dysfunction.[14] Furthermore, preirradiation treatment with multiple chemotherapeutic agents does not further increase the incidence of thyroid dysfunction.[14]

We found a low incidence of hypothalamic-pituitary-adrenal dysfunction (7%) after fractionated total body irradiation compared with the incidence of 24% reported by Sanders *et al.*[4] The adrenal gland is relatively radioresistant and impairment of corticotrophin secretion is not seen in children receiving 1800–2400 cGy cranial irradiation prophylactically for acute lymphoblastic leukaemia.[15] The high incidence in the report by Saunders *et al* may be due to the suppression of the hypothalamic-pituitary-adrenal axis associated with the previous use of high dose steroids to treat either the undelying condition or graft-versus-host disease.[4] Moreover, use of the metyrapone test, which has been shown to have a significant failure rate in normal individuals,[16] may also explain the high incidence of cortisol deficiency previously reported.[4]

Severe gonadal damage is common after total body irradiation. All girls of pubertal age at time of assessment had ovarian failure irrespective of their pubertal status at the time of irradiation. Although the ovary is less sensitive to the effects of irradiation than the testis, the LD_{50} (the radiation dose causing death to 50% of oocytes) has been estimated to be less than 400 cGy.[17] A similar incidence of ovarian failure is reported after single fraction total body irradiation.[3]

Most of the boys exhibited severe damage to the germinal epithelium yet none had overt Leydig cell failure. There is evidence to show that the germinal epithelium of the testis is more vulnerable to the effects of both cytotoxic chemotherapy and irradiation than either the ovary or the Leydig cell.[18] Therefore the universal finding of damage to the germinal epithelium would be anticipated after both gonadotoxic chemotherapy and irradiation. Germ cell dysfunction induced by similar conditioning chemotherapy and total body irradiation administered as a single fraction appears to be amenable to recovery as demonstrated by a return to normal of the previously raised FSH concentration with time, although semen analysis was not performed.[19] Animal evidence suggests that irradiation administered as a fractionated schedule is more deleterious to spermatogenesis than the same total irradiation dose in a single fraction. Recovery of spermatogenesis has, however, been described in adults who received fractionated total body irradiation.[2]

Unlike the testis, fractionated irradiation is less damaging to the ovary than single fraction irradiation,[20] although such differences may be lost at the doses employed in total body irradiation. In addition, all the girls in this study received a combination of gonadotoxic chemotherapy and fractionated irradiation, both of which may contribute to the development of ovarian failure. Recovery of ovarian function with time has been reported after both fractionated and single fraction total body irradiation,[4] and in our study one girl showed evidence of recovery of ovarian function two year after total body irradiation.

In conclusion, 80% of children had evidence of endocrine dysfunction a mean of 2·4 years after total body irradiation administered in a fractionated schedule. In such children there is a wide range of endocrine disturbance affecting the hypothalamic-pituitary axis, the thyroid, and the gonad. Close and early involvement of an endocrinologist in their management is mandatory.

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Is hearing assessed after bacterial meningitis?

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Abstract

A questionnaire was sent to 686 paediatricians in the UK to discover whether or not they referred children for hearing assessment after bacterial meningitis and if not, why not; 90% replied. Of these, 10% did not refer all children. The reasons given were based on misunderstandings of the aetiology and not on a lack of provision.

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Bacterial meningitis is still a serious and not uncommon infection in childhood. The mortality rate has fallen to below 10%[1 2] but is still significant and is higher in neonates.[3] The prevalence of neurological sequelae is also high.[4] The incidence of hearing impairment after bacterial meningitis has been reported to be anything from 6 to 31% depending on the type of meningitis studied and the type and severity of hearing impairment included.[5]

Total hearing loss is devastating to the development of speech, particularly in very young children when its presence may go undetected. Partial or unilateral hearing impairment in children of all ages likewise may go undetected as the child unknowingly compensates and vital stimulation may be missed, particularly in the early years at school.[5]

This study was designed to discover what provision is routinely made for hearing assessment after treatment for bacterial meningitis in the UK.

Methods

A questionnaire was sent to each of the 686 members of the British Paediatric Association practising in the UK. A reminder was sent to non-respondents four weeks later.

The questionnaire was short. The key question was 'Do you routinely refer *all* children recovering from bacterial meningitis for formal hearing assessment?' If the answer was 'No' the respondent was asked to give his or her reasons with three closed choice suggestions and two open ended ones. If the answer was 'Yes' the respondent was asked to indicate how long after discharge from hospital the child would routinely be referred. Finally, there was an opportunity to make additional comments on postmeningitic hearing problems.

Results

The response rate to the first mailing was 75·4% (n=518). One reminder boosted this to 90·1% (n=619). This exceptionally high response for a survey of practice means that the results are highly representative.

Of the 613 replies to the first and main question about routine referral, 504 said that they did refer all children recovering from bacterial meningitis for formal hearing assessment, 60 that they did not, and 49 stated that they never saw children with acute meningitis (six replies missing). Thus, 504 of the 564 (89·4%) paediatricians who routinely see children with bacterial meningitis claim to refer all for formal hearing assessment.

The 60 (10·6%) who answered that they did not routinely refer all children recovering from bacterial meningitis for formal hearing assessment gave reasons as shown in the table. There was no case where the reason for non-referral was a cited lack of available relevant skills for hearing testing in young children. The 32

Reasons given for non-referral by 60 respondents answering that they did not routinely refer all children recovering from bacterial meningitis for formal hearing assessment (total more than 60 as more than one reason could be given)

Reason for non-referral	*No (% of 60 responses)*
(a) Feel it is generally unnecessary to do formal hearing tests following bacterial meningitis	8 (13·3)
(b) Only refer children where there is already some concern over their hearing	38 (63·3)
(c) Only refer for hearing tests those children who meet some other criterion	27 (45·0)*
(d) The relevant skills for hearing testing in young children are not available	0
(e) Other reason	5 (8·3)*

*Other reasons given:

Age	*No*	*Severity*	*No*	*Bacterium*	*No*
<10 years	1	More seriously ill	10	Severe meningococcal	1
<5 years	5	Complications	3	*Haemophilus influenzae*	1
<3 years	2	Purulent discharge	1	Pneumococcus	2
<2 years	2	Impaired speech	1	*Haemophilus influenzae* and pneumococcus	3
<1 year	1	Raised intracranial pressure	1		
<6 months	1				

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respondents who answered positively to parts (c) and (e) based their decision on age, severity of the illness, and/or the infecting organism.

Of the 504 positive reports of routine referral, 271 (53·8%) claimed to refer children immediately on discharge, 230 (45·6%) at the first outpatient appointment, and three (0·6%) at some later time. The responses indicate that about 60% of children are referred within three months and all within a year of discharge.

The majority of the additional comments about postmeningitic hearing impairment (n=62) indicated that cases of hearing impairment were seen very infrequently, eight respondents having never seen a case. Other comments concerned factors possibly associated with hearing impairment (n=28). Some of these were based on misunderstandings of the aetiology. Thirteen respondents stated that hearing impairment *only* followed infection with *Streptococcus pneumoniae* or *Haemophilus influenzae*. At least three doctors thought that the referral was not urgent and one thought that the routine distraction test of hearing at 8 months was a sufficient safety net for children younger than this age.

Comments in 25 cases concerned problems with assessing the children including long waiting lists for audiology, lack of direct access to the audiology service, and the lack of age appropriate testing skills.

Discussion

The results of this survey are very encouraging. They indicate that, in general, paediatricians are aware of the need for formal hearing assessment and are including this as part of their routine management. It is to be hoped that these good intentions are always translated into good practice.

The results indicate that doctors who say that they do not always refer are basing their decisions most often on a clinical concern over the child's hearing. This implies that paediatricians are acting as the first screen of hearing ability after bacterial meningitis. The accurate bilateral testing of young children is difficult even in the best surroundings and impossible in a busy ward or outpatient clinic. A child who appears to hear in such circumstances may none the less have a mild to moderate bilateral or a unilateral impairment.

Whether age is an appropriate referral criterion must be determined from good quality epidemiological data, but no satisfactory study so far supports the restriction to those under 3 years. This cut off would not reduce the workload of the audiological services by an appreciable amount as the majority of cases occur under this age, but it would mean that some children with damage to their hearing would be missed.[6]

Referral based on the bacterium responsible would also miss some children with hearing impairment as hearing impairments have been found after meningitis due to each of the major infective organisms.[6]

In our view, when to refer postmeningitic children should not be in question. Referral should be made while the child is still in hospital and the importance of the assessment stressed to the parents. The assessment should ideally take place four to six weeks after discharge to allow for resolution of any associated conductive impairment and to ensure that profound hearing impairments are detected early enough to enable a cochlear implant to be a viable option.

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Toxic shock-like syndrome caused by adenovirus infection

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Abstract

Adenovirus infections commonly occur in childhood and produce a wide range of clinical disease. The most common sites of infection are the respiratory and gastrointestinal tracts but involvement of cardiovascular, neurological, cutaneous, ophthalmic, renal, and hepatic systems can also occur. A case of toxic shock-like syndrome with symptoms of multiorgan involvement resulting from adenovirus infection is reported.

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Case report

Four weeks after returning from a two month holiday in the Philippines and Australia a 5 year old girl developed abdominal pain, fever, and vomiting. Over the subsequent four days she developed an erythematous maculopapular rash on her abdomen, profuse watery diarrhoea, and was admitted to the referring hospital. At the initial examination she had fever, cervical lymphadenopathy, and was dehydrated. She was rehydrated with normal saline and started on flucloxacillin and cefuroxime. Over the next 24 hours her serum sodium concentration dropped from 129 to 115 mmol/l despite good renal function. Her haemoglobin concentration was 11·4 g/l, white cell count increased from $9{\cdot}3\times10^{9}$/l to $19{\cdot}1\times10^{9}$/l, and her platelet count fell to 93×10^{9}/l. Her tissue perfusion deteriorated and metabolic acidosis developed requiring circulatory support with dobutamine and colloids. She was referred to the intensive care unit, Hospital for Sick Children, Great Ormond Street, for further management.

On arrival she was febrile with a temperature of 39·5°C. She had an erythematous rash over her trunk with target lesions similar to erythema multiforme, erythematous palms, fissured lips, and conjunctivitis. She was tachycardic and hypotensive (pulse 150/minute, systolic blood pressure 70 mm Hg) and had a cold periphery. She had peripheral oedema in her lower limbs and over her sacrum. She was breathing spontaneously in 50% oxygen with marked respiratory distress. On auscultation there were widespread crepitations in both lung fields. Her abdomen was distended and tender. She was disorientated and restless.

INVESTIGATIONS

Results of laboratory investigations are shown in the table. A chest radiograph showed cardiomegaly and pulmonary oedema. Her electrocardiogram was normal and an echocardiogram showed an enlarged poorly functioning left ventricle but no intracardiac structural abnormality.

Blood cultures taken before antibiotics were started were negative. An initial sample of cerebrospinal fluid contained a white cell count of 3/mm^3, protein concentration 0·33 g/l, and glucose 4·8 mmol/l. No organisms were seen and there was no growth on primary culture. Routine cutaneous swabs grew no pathogens and a malaria parasite slide was negative. Antistreptolysin-O titre was 100 Todd units and anti-DNAase titre 100 units.

In view of the fact that she had spent two months in the Philippines and Australia, serological testing for geographically relevant pathogens (including arboviruses) was performed and found to be negative.

PROGRESS

The clinical picture was compatible with a diagnosis of staphylococcal toxic shock syndrome. She required ventilatory support and suffered from severe hypotension and cardiac insufficiency requiring high dose dobutamine and dopamine to maintain her blood pressure. This high dose inotropic support was needed for three days, but as her cardiac function began to normalise support was able to be gradually reduced over the next four days. She was unconcious for three days with an electroencephalogram showing non-specific features of diffuse encephalopathy. It was thought that this was due partly to her underlying disease but also partly due to increased opiate sensitivity. A cranial computed tomogram was normal. Initially she had considerable abdominal distension, pain, and diarrhoea, and this gradually resolved over the next week. Nine days after admission she was extubated and all inotropic support discontinued. After a further two days she developed desquamation over the tips of all her fingers. She continued to improve and was discharged after 17 days in hospital with a diagnosis of staphylococcal toxic shock syndrome.

Results of laboratory investigations

Investigation	*Result*
Haematology:	
Haemoglobin (g/l)	7·9
White cell count ($\times10^{9}$/l)	13·5 (neutrophils 11·4)
Platelet count ($\times10^{9}$/l)	79
Biochemistry:	
Sodium (mmol/l)	127
Potassium (mmol/l)	2·8
Urea (mmol/l)	9·5
Creatinine (μmol/l)	80
Calcium (mmol/l)	1·68
Liver function tests:	
Albumin (g/l)	18
Total bilirubin (μmol/l)	28
Aspartate aminotransferase (U/l)	104
Creatine phosphokinase (U/l)	8130

However, after discharge a non-typable strain of adenovirus was isolated from culture of both the cerebrospinal fluid and urine specimens collected at her original presentation. Follow up serology demonstrated a rising CF titre of antibody to adenovirus from initially undetectable on admission, to 1:16 one month later and to 1:32 six weeks later. Immune function tests during convalescence showed raised serum IgG$_1$ (20 g/l, normal 3·2–7·6 g/l) and IgM (4·9 g/l), suggesting a recent infection, and normal serum IgG$_2$, IgG$_3$, IgG$_4$ IgA, IgE, complement, and normal T cell subsets and lymphocyte PHA responses. There was therefore no evidence of immunodeficiency.

Discussion

The toxic shock syndrome is a clinical diagnosis based on case definition.[1] There is no confirmatory laboratory test and the isolation of TSST-1 producing *Staphylococcus aureus* is not required to establish the diagnosis. Our patient satisfied the clinical diagnostic criteria for toxic shock syndrome in that she had fever 38·9°C, an erythematous rash, desquamation, and hypotension. She had additional involvement of the following organs and systems: central nervous system, gastrointestinal tract, skeletal muscle, heart, respiratory tract, liver, and her haematological system. She also had initial negative microbiological results to establish an alternative diagnosis. However, the subsequent growth of adenovirus from her cerebrospinal fluid and urine and her seroconversion confirmed disseminated adenovirus infection.

Adenovirus infection can involve many organ systems, but the respiratory and gastrointestinal tracts and conjunctiva are most frequently involved. The skin, heart, central nervous system, skeletal muscles, liver, and kidneys are occasionally involved.[2] It is, however, very uncommon for a single adenovirus strain to produce multisystem disease in an apparently immunocompetent individual. This case had multisystem involvement, some of which may be explained by the effects of shock, but the skin changes, the central nervous system involvement (with adenovirus cultured from the cerebrospinal fluid), the skeletal muscle involvement (with a creatine phosphokinase of 8130 U/l), and the myocarditis cannot be attributed to hypotension alone. We therefore believe that she had disseminated adenovirus infection producing a clinical picture identical to that of staphylococcal toxic shock syndrome.

Toxic shock-like syndrome has been described with several infectious agents, including staphylococcus,[3] streptococcus,[4] and pseudomonas[5]. The toxins which cause staphylococcal and streptococcal toxic shock syndrome have a common mode of action, binding to specific Vβ bearing T cells and stimulating T cell proliferation and cytokine release.[6] It is possible that similar immune events were induced by adrenovirus infection in this child.

We conclude that this case with multiorgan involvement producing a clinical picture of toxic shock syndrome was due to infection with adenovirus. We therefore recommend that clinicians consider adenovirus infection in the differential diagnosis of toxic shock syndrome in children.

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Accidental ingestion of 'Ecstasy' (3,4-methylenedioxymethylamphetamine)

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Abstract

There is no report of the effects of 'Ecstasy' (3,4-methylenedioxymethylamphetamine) poisoning in childhood. The case of a 13 month old boy who ingested one capsule of Ecstasy is reported. Neurological and cardiovascular side effects predominated, which responded well to treatment with a chlormethiazole infusion.

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Recreational use of 'Ecstasy' or 'E' is common particularly within the confines of acid house parties. Chemically Ecstasy is 3,4-methylenedioxymethylamphetamine (MDMA). MDMA is a psychoactive phenylisopropylamine, chemically related to both amphetamine-like stimulants and hallucinogens such as mescaline, and is reputedly safe. The usual dosage is 50–150 mg, and the duration of action is 4–6 hours. The drug reportedly induces a state of enhanced self awareness and ability to communicate, without distorting normal thought processes.[1] Increasing use by young people has been documented,[2] but our report and those of fatal or serious side effects in teenagers and adults[3–5] must caution against the belief that this drug is safe.

Case report

A 13 month old boy was admitted with a history of ingesting a capsule of Ecstasy found on the floor 30 minutes previously. He was in the care of his grandmother at her home while his mother was at work. His uncle, who was present, freely admitted to recreational use of the drug in this home where he also lived, but not on the evening in question.

The clinical features are summarised in table 1. The convulsion was unresponsive for 60 minutes to a total of 2·5 mg/kg diazepam and 0·4 mg/kg of haloperidol, both given intravenously. A chlormethiazole infusion (10 mg/kg/hour) was commenced and there was a dramatic response with both the convulsion and the cardiovascular instability resolving within 5–10 minutes. A further self limiting episode of hypertension (180/70 mm Hg) and tachyarrhythmia (170 beats/min) occurred five hours after admission. All abnormal signs had resolved by seven hours so the chlormethiazole infusion rate was halved and finally stopped at 16 hours.

No haematological or biochemical abnormalities were observed. Results of toxicology are shown in table 2.

The possibility of non-accidental ingestion of

Table 1 Clinical features attributed to MDMA

Initial findings
Generalised shaking
Dilated pupils
Hypertonia
Writhing and jerking movements
Within one hour
Convulsion
Tachyarrhythmia (70–170 beats/min)
Hypertension (maximum 120 mm Hg systolic pressure)
Fever (maximum temperature 38·5°C per axilla)

Table 2 Toxicology on admission. Time represents interval since ingestion

Serum (at 90 minutes)	MDMA	0·7 mg/l
	MDA	<0·1 mg/l
Urine (at 2 hours)	MDMA	Detected
	MDA	Detected
	Chlormethiazole metabolites	Detected
	Other basic or neutral drugs	Nil

MDMA was a foremost consideration and social services staff were therefore involved at an early stage. Prompt presentation in the early evening and a clear, consistent history from carers who themselves had no signs of MDMA ingestion resulted in the conclusion that the episode was accidental.

The child recovered completely and was discharged four days after admission to the care of his mother, with social service follow up and strong advice regarding the safety of drugs in the home. He had no short term neurological deficit but was subsequently lost to medical follow up.

Discussion

Animal studies show that MDMA reduces 5-hydroxytryptamine and 5-hydroxy indoleacetic acid concentrations at nerve terminals, and the metabolite 3,4-methylenedioxyamphetamine (MDA) selectively destroys 5-hydroxytryptamine nerve terminals. MDMA also increases dopamine turnover, this being implicated in the long term neurotoxicity of MDMA use. The dopamine receptor antagonist haloperidol and some 5-hydroxytryptamine antagonists are effective in blocking these actions,[1] hence the recommendation of haloperidol in the treatment of side effects.

Four fatalities in adults related to Ecstasy abuse have been reported, with recorded MDMA concentrations between 0·2 mg/l and 1·1 mg/l; one patient survived with a concentration of 7·0 mg/l.[3–5] Fatalities have been associated with cardiovascular autonomic derangement and in one case coagulopathy and hyperthermia. The exact cause of the latter complications is unknown, but MDMA induced 'oxidative stress' may play a part.[1] Alternatively coagulopathy and hyperthermia may be linked to the circumstances of the ingestion, be idiosyncratic reactions, or the result of unidentified impurities in the manufacturing process.

In addition, the effects of amphetamine induced hyperthermia are similar to the effects of heatstroke and include derangements in coagulation.[6] Rapid control of the rising temperature in our case may have prevented coagulopathy occurring by a similar mechanism.

Controlling the seizure proved the major problem in this child. Chlormethiazole infusion brought about rapid control not only of the convulsion, but also of tachyarrhythmia and hypertension. Chlormethiazole may have acted by potentiating the effects of the inhibitory neurotransmitters γ-aminobutyric acid and glycine. Serotonergic mechanisms and dopamine inhibition are possibly secondary.

In conclusion Ecstasy is not a 'safe' drug. It is a drug of abuse and must at least be stored safely away from children We suggest that chlormethiazole may have a role in controlling toxicity from MDMA.

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CONTROVERSY

Avoiding chemotherapy related late effects in children with curable tumours

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A number of articles have highlighted the dilemma facing those involved with the design of treatment programmes for patients with curable tumours, in whom long term survival necessitates the avoidance, if possible, of late sequelae.[1 2] Nowhere is this problem more apparent than in the management of paediatric cancer. With almost 60% of children who have been treated for cancer in the past decade achieving long term survival and probable cure, it is becoming increasingly clear that a variety of problems are being created as a direct consequence of curative treatment. Many paediatric subspecialists other than oncologists, such as endocrinologists, cardiologists, respirologists, and neurologists are involved in the joint long term follow up of these children into adulthood. The problem of avoiding mutilating surgery has largely been achieved by the use of preoperative chemotherapy. Similarly, extended field high dose radiotherapy is now rarely used in paediatric practice. These improvements that avoid late sequelae are, however, dependent on the effective use of chemotherapy to achieve maximum response and reduce or obviate the need for further treatment directed towards local tumour control.

In an attempt to reduce chemotherapy related late sequelae there is at present considerable debate concerning which drugs could be dropped or replaced by less toxic agents. Virtually all chemotherapeutic agents are non-specific cell poisons; their effectiveness often depending on a narrow therapeutic ratio (that is, tumour cell kill to normal tissue toxicity). Up until recently the classic 'bogymen' of chemotherapy were the alkylating agents. The use of regimens such as mustine, vincristine, procarbazine, prednisolone (MOPP) or chlorambucil, vincristine, procarbazine, prednisolone (ChlVPP) in childhood Hodgkin's disease is undesirable if effective alternatives exist because of the inevitable sterilising effect in males and the possible risk of second tumours and leukaemia. There is little doubt about the sterilising effect in boys after standard chemotherapy for Hodgkin's disease, although girls are generally spared this adverse effect.

Data for cyclophosphamide alone are less clear, but it seems likely that a third to a half of boys will be sterilised after conventional 12–24 months regimens for various childhood solid tumours.[3] It has been suggested that a total cumulative dose of up to around 4 g/m^2 of cyclophosphamide can be given without sterilisation.[4–6] With regimens containing a small number of courses using high doses of cyclophosphamide, for example in non-Hodgkin's lymphoma, where up to 3 g/m^2 is given per course,[7 8] the sterilising effect may be less than when the same total dose is given over several months. This remains to be clarified, however, in prospective studies. Ifosfamide, an analogue of cyclophosphamide, which appears to be less myelosuppressive with comparable antitumour alkylating activity, is now in widespread use for Ewing's sarcoma, rhabdomyosarcoma, and some protocols for leukaemia/lymphoma. Unfortunately the lack of myelosuppression has been offset by a disturbing incidence of renal tubulopathy. The precise incidence of significant dysfunction remains unclear pending adequate studies of unselected patients, but there is little doubt that a Fanconi-like syndrome may occur particularly in the smaller child who has received high doses of ifosfamide. The sterilising effect of four to six courses of 6–9 g/m^2 ifosfamide is unclear but seems likely.

The incidence of second cancers in children ranges from 1–4% and is dependent on the nature of prior chemotherapy and the use of radiotherapy.[9] In adults an incidence of up to 18% at 15 years has been reported in those with Hodgkin's disease who have received alkylating agents and radiotherapy.[10] In one study of childhood Hodgkin's disease using an alternating MOPP/doxorubicin bleomycin, vinblastine, dacarbazine (ABVD) regimen where the median follow up was only 35 months three out of 62 patients developed second malignancies. The latter attempt to reduce the late effects of a MOPP based regimen could in fact result in 'the worst of both worlds', namely sterilisation, second tumours, anthracycline related cardiotoxicity, and bleomycin related lung toxicity.[11] With a conservative radiotherapy policy risks are lower and only three second malignancies have occurred in 232 children mostly receiving ChlVPP alone on the current United Kingdom Children's Cancer Study Group (UKCCSG) regimen. High incidences have been reported in children with Ewing's sarcoma treated with cyclophosphamide based regimens and high dose radiotherapy[12] and in children with non-Hodgkin's lymphoma receiving cyclophosphamide and chloroethylcyclohexyl nitrosourea (CCNU) regimens.[13]

In solid tumours such as rhabdomyosarcoma and Wilms' tumour a series of prospective randomised studies have evaluated the need to include cyclophosphamide. The American Intergroup Rhabdomyosarcoma Study group has demonstrated clearly that this drug is not necessary to cure patients with completely resected rhabdomyosarcoma or in those with microscopic residual disease provided they are irradiated.[14 15] In the case of Wilms' tumour, cyclophosphamide is not required but with more extensive tumour the omission of this agent must be off set by the retention of an anthracycline; this is a debatable compromise.[16]

In non-Hodgkin's lymphoma the overall cure rates now exceeds 80% and the necessity for including cyclophosphamide is currently being evaluated by the UKCCSG. In the UKCCSG 9001 regimen children with localised (Murphy stage 1 and 2) disease receive a non-alkylating agent regimen that does include an anthracycline. The French paediatric oncology group has reduced the duration of chemotherapy to two courses of cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP) for patients with stage 1 and 2 disease in the hope that the total dose of alkylating agent and anthracycline will be sufficiently low to avoid late effects. The American CCSG has opted to omit the anthracycline using the cyclophosphamide based cyclophosphamide, vincristine, methotrexate, prednisolone (COMP) regimen. Which of these options is preferable will only become apparent with further follow up in each study when information regarding sterility and cardiotoxicity is available. Attempts to avoid the alkylating agents in Hodgkin's disease include the ABVD and vincristine, etoposide, epirubicin, and prednisolone regimen. ABVD has the disadvantage of potential lung toxicity from bleomycin and doxorubicin cardiotoxicity. In VEEP chlorambucil and procarbazine are replaced by etoposide and epirubicin, which are non-sterilising, and it was hoped that the late cardiotoxicity of epirubicin would be less than with doxorubicin.[17] The ABVD regimen has been shown in both adults and children to be equally effective to MOPP or ChlVPP. With VEEP, however, although response rates in adults have been comparable with that seen with the ChlVPP regimen, this has not been the case in a pilot childhood study where the incidence of initial refractory disease has been worrying.[17] The strategy of using an etoposide based regimen relies on a high salvage rate, in the event of failure, using ChlVPP and radiotherapy. In this way even if there is a higher relapse rate using the VEEP regimen the overall cure rate should be comparable but the majority of boys will not be sterilised and it is hoped that second tumours will be fewer. This approach remains controversial as it involves potentially suboptimal treatment in order to avoid sterility, which should be effective in most, but accepts that the minority who relapse will end up having even more intensive treatment to achieve cure. This therefore raises the issue of how important is fertility?

Recent evidence on late effects of anthracyclines is one of the most worrying aspects of paediatric chemotherapy.[1 2 18] Up until recently it was felt that a cumulative dose of up to 350 mg/m^2 of doxorubicin was 'safe' and such doses may be included in regimens for acute lymphoblastic leukaemia, acute myeloid leukaemia, and Ewing's sarcoma. This now appears to have been an underestimate. For a number of years there have been anecdotal reports of children treated for solid tumours developing cardiac insufficiency during pregnancy or after severe exercise, but these patients had usually received high cumulative doses. The demonstration by sophisticated echocardiography of myocardial impairment in children with leukaemia who have received considerably less than the conventional safe dose suggests that this may not in fact exist. Unfortunately at present no reliable method of monitoring cardiac function during treatment allows cessation of anthracyclines before significant damage occurs. Endomyocardial biopsy is the only definitive way to detect early anthracycline damage. For obvious reasons data are very limited in children and interpretation of any changes seen with regard to functional prognosis would be difficult. Electrocardiography or conventional echocardiography are only able to detect established damage. Recent improvement with M mode and colour flow Doppler may improve sensitivity but standardisation in methodology is required for multicentre use.

Strategies to try and reduce the cardiotoxicity of anthracyclines include prolonged continuous infusion schedules or the use of new analogues such as epirubicin, idarubicin, the substitution of doxorubicin with mitozantrone, or the use of cardioprotector drugs. In lymphoma or leukaemia where there are many potential active agents, the necessity for anthracyclines must be questioned. In the case of actue lymphoblastic leukaemia, there is little randomised study evidence supporting the need for this drug, particularly in the context of alternative combinations such as high dose cytarabine, etoposide, and high dose methotrexate. This issue needs to be urgently addressed in large national multicentre studies.

With solid tumours where non-cardiotoxic, non-sterilising agents such as cisplatin have activity, reluctance to use this drug because of its nephrotoxicity and ototoxicity may have been overcome by the introduction of its analogue carboplatin. There is, however, the trade off of a different toxicity, myelosuppression, that may result in dose reduction in combination treatment and thus have an adverse effect on efficacy. Moreover, the comparable activity of carboplatin needs to be clearly demonstrated in each of the relevant solid tumours.[19]

What other group of drugs should be considered to replace the major offending agents? Unfortunately most of the antimetabolites, such as methotrexate and cytarabine, which have few late sequelae have limited activity in solid tumours. Although well tolerated, the use of bleomycin in lymphomas or germ cell tumours is to be avoided because of the late effects on pulmonary function. It is likely that this drug will be omitted completely from most paediatric schedules in the near future once it has been demonstrated that its inclusion in the PVB (cisplatin, vinblastine, bleomycin) or BEP (bleomycin, etoposide, cisplatin) germ cell tumour regimen in adults is not necessary, provided sufficient doses of the other drugs are given.

The epipodophyllotoxins, etoposide or teniposide, have achieved popularity in recent years with demonstration of activity in leukaemia, lymphoma, Wilms' tumour, rhabdomyosarcoma, and neuroblastoma. Continuing studies are evaluating the precise role of etoposide but its apparent lack of late effects made it a very attractive agent to replace alkylating agents and anthracyclines in many tumours. These hopes have been somewhat dampened recently by reports describing an apparent increase in secondary leukaemias in patients treated with teniposide/etoposide based regimens for both solid tumours and leukaemia. In a number of these reports etoposide has been given in combination with alkylating agents, making it difficult to be sure about its precise contribution. In small cell lung cancer and malignant germ cell tumours etoposide or teniposide do appear to be implicated.[20 21] In these reports the dose of etoposide has been higher than that currently used in most paediatric protocols. There have to date been very few reports of secondary leukaemias in children given etoposide or teniposide for solid tumours.[22] In one frequently quoted study where a high incidence of secondary acute myeloid leukaemia was observed after treatment for non-Hodgkin's lymphoma, in addition to teniposide the well known carcinogen CCNU was included in the protocol.[13] There has, however, been some more convincing evidence in childhood acute lymphoblastic leukaemia where the schedule of etoposide and teniposide appear to be important. Children receiving frequent administration of these agents, that is once or twice a week, appeared to be at significant risk.[23] Again the total doses were considerably greater than those used in solid tumours with a median total dose of $6/m^2$ in those affected, with only one case occurring with a total dose of <3 g/m^2. The high percentage of cases with involvement of chromosome 11 q23, which has been observed after in vitro treatment of cell lines with etoposide,[24] is further supportive evidence of its 'leukaemic' effect when given at high doses.

In patients with acute lymphoblastic leukaemia there was no increased risk for children given etoposide on an alternate weekly basis, and where the drug is given once every three weeks as in most solid tumour regimens it is likely to be safe. There is, however, evidence that the more frequent scheduling of this agent may be more effective.[25 26] It is probably wise to limit such regimens to those with high risk disease or after relapse where improved efficacy could outbalance the small but significant risk of transforming mutations in normal myeloid progenitor cells.

In conclusion, it is clear that we cannot expect effective curative chemotherapy to be devoid of all late sequelae. There are, however, children with tumours where at present the cure rate exceeds 70%, for example, acute lymphoblastic leukaemia, Wilms' tumour, malignant germ cell tumours, non-Hodgkin's lymphoma, Hodgkin's disease, and localised soft tissue sarcomas. For these patients protocol design will rest upon whether one accepts infertility rather than the risk of late cardiomyopathy or if soft tissue and bone hypoplasia due to localised radiotherapy is preferable to a small risk of chemotherapy related second leukaemias. This is a topic of intense debate among paediatric oncologists and many of the points raised require clarification. Because of the comparatively small number of patients involved and the high cure rates seen, prospective randomised studies evaluating the effect of omitting potentially toxic agents or the alternative late effects of newer drugs need to be done on a large multicentre, probably international, basis. The International Society for Paediatric Oncology, SIOP, is one forum where this could be done and should be encouraged to start in the near future. Empirical changes without adequate prospective evaluation may lead to replacing one toxicity by another unexpected one—out of the frying pan, into the fire.

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Dyslexia

It has always seemed to me that some people make very heavy weather of dyslexia. 'Do you believe in it?' they say, as if it were a cross between astrology, water divining, and Rosicrucianism. Of course I believe in it. The fact that some people of normal or high intelligence have inordinate difficulty with reading is a matter of experience as easily verifiable as the fact that some people have eyes of different colour. Ah, well if it exists, is it a *disease?* The *New England Journal of Medicine* of 16 January 1992 includes a leading article with that title, 'Dyslexia—is it a disease?'[1] We could get into deep water by pursuing the question of what constitutes a disease but in the context of this article the point at issue is whether children who have reading skills which are inappropriately low for their intelligence represent simply the lower end of a normal distribution curve or whether they are a separate group with distinct pathophysiology.

In the same issue of the *New England Journal of Medicine* there is a paper from Yale (Sally E Shaywitz and colleagues, 1992;**326:** 145–50) which attempts to answer this question. The Connecticut Longitudinal Study is a follow up study of 414 children who began their schooling in 1983. They had intelligence tests performed in their first, third, and fifth school years and annual tests of reading and mathematical proficiency in their first six years at school. When reading scores were compared with full scale IQs it was apparent firstly that as expected, there is in general a fairly close correlation between intelligence and reading ability. Secondly, the distribution of reading scores for IQ seemed normal and these workers were unable to detect a 'hump' at the lower end of the scale. They conclude that there is a smooth normal distribution curve for reading ability in relation to intelligence and that children with dyslexia represent the lower end of this normal distribution, the cut off between normal and abnormal being arbitrarily defined. This does not exclude a small number of children having a pathological cause. They estimate that if the prevalence of pathological dyslexia were 5% their study would have a 90% chance of detecting a hump but at a prevalence of 0.5 to 1% their chance of showing a hump would be less than 20%. So these data suggest that either there is no pathological dyslexia or its prevalence is less than it has been thought to be.

Dyslexia due to a specific defect of neuroanatomy or neurophysiology might be expected to be fairly constant but in this study there was considerable variation with time. Defining dyslexia as a reading score more than 1·5 SDs below that expected for intelligence there was considerable movement from year to year in and out of the dyslexic group. Thus, of children defined as dyslexic in the first school year only 28% were still so defined in the third year and of those dyslexic in the third year 47% were still dyslexic in the fifth year. Equally, some children not dyslexic in the earlier school year became so later. A considerable number of children had reading scores well in advance of their intelligence. Were they superlexic? Clearly, if reading ability for IQ is normally distributed then dyslexia and superlexia should be equally prevalent. I've never heard of superlexia. Could it give rise to any problems?

What are the implications? There can be no doubt that some children underachieve as regards reading and need help. There may be a small hard core of children with stable dyslexia who need constant help but other children's reading achievement may fluctuate and they may need help at different times in their school careers. Reading disability, it seems, cannot be diagnosed once and for all in the early school years.

ARCHIVIST

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Archives of Disease in Childhood 1992; **67**: 1120–1123

TYPES OF PSYCHIATRIC TREATMENT

Inpatient psychiatry units

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This is the eighth of a series of articles on treatment of child psychiatric disorders.

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Inpatient child psychiatry should be seen as a mode of treatment and not a bureaucratic convenience or a form of substitute care. The kind of therapeutic work and research generated within inpatient units has taken a distinguished place in the history of mental health services for children,[1] but in the current climate there are a number of trends that quite rightly necessitate those of us working in such units to clarify and define our role in current mental health services for children. In both paediatrics and adult mental health there has been a move away from inpatient beds and towards primary care and community services. In child psychiatry a family oriented approach can make isolating the child during an admission seem paradoxical. Our units, although low on medical technology, have high needs for staffing and physical fabric, and can seem expensive.

As in any mode of treatment one can consider indications for use, mode of action, appropriate 'dosage', efficacy, and unwanted effects. I will also try and speculate a little into the future. The focus of this article is child inpatient units for children up to 14 years; adolescent psychiatry units taking children from 14 upwards have their own particular features, although many of the same points apply.

Indications for inpatient treatment

Most admissions would fall into one of these groups:

(1) Problems for which outpatient treatment is felt to be insufficient or impossible and where there is a need for the intensity, completeness, or safety of residential treatment involving nursing staff. The child's disorder is sometimes life threatening, usually severe or persistent: such as serious depression or suicidal risk, eating disorder, obsessional disorders, intractable soiling, psychotic illness, or hysterical conversion.

(2) Problems where the nature of the difficulties are unclear and residential assessment could be a valuable aid in clarifying diagnosis and needed treatment. Examples here would be some severe emotional disorders with complex family pathology, autistic-like syndromes, neuropsychiatric disorders where the balance between organic and psychological factors is unclear, and assessment of parenting, especially where there are specific concerns about risk to the child (for instance in Munchausen syndrome by proxy).

(3) Crisis situations in which psychological disorder in the child or family has reached such a pitch that caring has broken down, the child is at risk, and the referrer highly concerned. This is the unit as 'asylum'. An important distinction has to be made here between family breakdown in the context of psychiatric treatment, and care and control issues where reception into social services care would be more appropriate.

(4) Occasionally, admission for controlled trials of drug treatment such as stimulants or supervised alteration of antipsychotic or anticonvulsant medication.

Despite calls from within the profession for more consistency,[2 3] inpatient units have often tended to develop idiosyncratically according to local conditions and personalities. Many units will develop particular areas of expertise and thus generate referral biases. I think it it crucial for the legitimacy of these scarce (usualy supradistrict) resources, however, that they maintain the flexibility to respond to the full range of referrer need.

How are inpatient units therapeutic?

FAMILY ORIENTATION

Traditionally, many residential units created communities which were an 'alternative world' for the child during the course of very long admissions. The intention was for children to experience a specialised social life that would allow them to recover from a traumatic environment outside. Ordinary social expectations would often be suspended in the service of therapeutic effect. Homer Lane's 'Little Commonwealth' embodied this view, which has links with the movements within progressive and special education in the first part of the century such as Summerhill and Dartington Hall.[1] Such environments can be valuable and still exist,[4] but on the whole not within the health service. Current psychiatric units, on the contrary, see themselves as far more integrated with the child's environment and wider service provision.[5] This is particularly the case in relation to the family. We face two ways: inwards towards providing a specialised therapeutic environment for the child and outwards towards preparing the family from the outset for the child's return. This Janus faced position is arduous but essential to maintain. The paradox of removing children from home the better to restore them to it runs right through the way our practice is organised, and the implications of working with parents under the new UK Children Act has only strengthened our need to do this. Some children will present as adrift, effectively without a recognisable 'family': decisions here can be most difficult. We will insist that a 'home base' with responsible adults be identified before reconsidering admission.

THE DISLOCATION EFFECT

Children become resident for substantial lengths of time (mean length of admission in my unit is about eight weeks but many treatment admissions will extend for four months or more). This time away from family and school can have profoundly useful consequences. The children have a chance to experience themselves in a therapeutic environment. The family have a chance to recover and change without the continual pressure of the crisis. Their reintegration can be managed therapeutically.

THE ADMISSION PROCESS

We maximise the therapeutic potential of this 'dislocation' by the considerable work that goes on before the admission in assessing the family and negotiating with them and the referrer about the reason for it. Problems are clarified, general aims are set, and the responsibilities of other family members to work with the unit during admission are defined. Sometimes a formal 'contract' is produced and signed. As Bruggen *et al* have described this preadmission work can be very effective at focusing minds and sometimes obviates the necessity for admission at all.[6 7] This is worth stressing because referrers to inpatient units (as well as families) often expect an immediate admission rather along the model of the medical ward and may feel frustrated by what are seen as obstructive preadmission procedures.

An emergency admission service is nevertheless available, and children can be assessed and admitted within a few hours when necessary. After such an admission the usual preadmission procedure will still be undertaken before a further commitment is made to keep the child for longer therapy.

THE UNIT AS PARENT

Theoretical writing on inpatient units has tended to oscillate between seeing the ward environment as a neutral background to specific treatments,[5] or as the major therapeutic agent in itself. The ward has been developed to function therapeutically in two major ways. In the therapeutic community model, derived from pioneering work after the war in adult psychiatry, the living among other patients and staff itself, when properly supervised and explored in groups, is seen to have a major role in social learning and psychological readjustment.[8] In a ward organised around behaviour modification (such as the 'token economy') contingencies on paticular behaviours are completely controlled so as to produce specific change in that behaviour.

In its extreme form, I do not think that the therapeutic community approach is appropriate for young and disturbed children whose major lack has often been good parenting; on the other hand the behaviour modification model, while useful symptomatically, really does not address the deeper needs of most of our children. I prefer to think of the unit as 'parent'; that is supplying for these children, albeit in an institutional context, the kind of adult behaviour that we know constitutes effective parenting. Elements of this will be: consistency of approach, good communication between the adults, clear communication of expectations and boundaries, firmness without retaliation or aggression, and the provision of appropriate privacy and time for intimate nurturing and physical care. Parenting is a complex series of skills. Most parents use at various times short range tactics aimed at rapidly modifying behaviour (the promise of a treat, a raised voice); medium range strategies involving organisation in space and time for children and communicating clear expectations; and long range goals, at the deepest level, to foster attachments and relationships. I see the unit doing likewise. We use behavioural methods in a planned way to modify specific behaviours. We recognise that the organisation and purposefulness of the environment can reduce unnecessary aggression and promote positive group dynamics. We then make space for privacy and individual nurturing that responds to the children's need for attachment and intimacy, recognising that this is often the deepest level at which they have suffered. The ward milieu remains basically 'reality orientated', and deeper levels of regression and acting out are generally expected more in the specific environment of an individual psychotherapy. The importance of peer relationships can be fostered by means of community groups and joint projects. Within such an environment, we find no need for a 'time out' room, in the behaviour modification sense, we use a supervised quiet room for children to 'cool down' when group tensions become explosive.

From the technical point of view, to preserve this kind of 'parental' stance in the face of assaults, retaliation, acting out, despair, and provocation from the children individually and more powerfully as a group, demands the highest quality of work. It dictates an organisation of the children into age orientated groups who have their own space on the unit and are worked with by a specific staff team. It demands maximum autonomy and devolved responsibility within that staff team: because the treatment is delivered essentially through individual relationships between adult and child, and these relationships are only possible for staff if they have a sense of personal responsibilty for their actions within shared treatment aims.[9] Leadership and supervision are needed from senior staff at all times.

It is thus a part of the ward's general healing function[10] to generate a *reality* of parental care, both in its own functioning and by working with parents. For many of our children, the experience of this is powerful therapy in itself, quite apart from any more specific treatments offered. It is a sad irony that the psychiatric ward is just the place where one often does not feel that hum of good will and parental involvement that is such a pleasurable feature of the paediatric ward; that it is psychiatric wards of all places that have often lagged behind in providing accommodation for parents. And yet this reflects a basic part of the problem of so many of our children, where the nature of the parental investment is low or problematic. Investment by the NHS often mirrors this neglect, and it is no coincidence that psychiatric wards are often shabby and hidden away 'around the back'. Management must be recruited effectively to counter this. It is a vital part of the treatment as the cared for environment sends a subliminal message of care to the children within it.[11] Bettleheim famously used the best cutlery and furnishings in his orthogenic school (even though they might not last long!) for just this reason.[12]

SPECIFIC THERAPEUTIC PROGRAMMES

The inpatient unit offers a range of more specific treatments. These will include individual child psychotherapy, behavioural programmes, medication, group work and creative work on the wards, work between parent and child, family work, and specific parent groups.[13] The unit's school is specifically for unit children and provides educational assessment and individualised teaching.

An important area of current development is in 'focal treatment planning'.[14–16] Goals are carefully defined before admission, treatments designed to accomplish these goals, and progress reviewed. This planning aims to avoid interminable treatment and therapeutic 'drift' by setting out achievable and measurable goals. In the Booth Hall unit, much work focuses around a number of assessment and treatment programmes—for instance a parenting programme, a programme for autistic-like social impairments, and a programme for over activity disorders. These programmes organise the staff into specific patterns of assessment and care, and because of their uniformity make research into treatment delivery and outcome much easier. They also present a clear service to referrers that can be costed. For children whose needs fall outside these programmes, the care plan will be individualised, but the goal orientation and monitoring is the same.

Unwanted effects of inpatient treatment

Like any powerful therapy, inpatient treatment can have unwanted effects.

It may prescribed in the wrong situation, and this is usually the result of inadequate preadmission assessment. The admission of a child of instance may simply collude with a scapegoating rejection by the family. Removal of a child from a local school for admission may take away the only source of real continuity and esteem that he or she has. The treatment may be continued too long and child and family may become demoralised or the child resigned to the institution or the sick role.

The dynamics of a unit can become unhelpful in a number of ways. Especially working with deprived groups, there is a tendency to become introverted and self contained, preoccupied with 'rescuing' children from an environment that is increasingly seen to be harsh and uncaring. Attitudes can drift into 'parent blaming' (P S Penfold, presentation to 9th Congress of the European Society for Child and Adolescent Psychiatry, London 1991), longer admissions, and anxious over protection of the children; in effect a substitute care. We work against this tendency by the involvement of ward staff in community visiting and home visits, and the active engagement of families into treatment along side the child. Of course, the reality *is* often appalling. We have to recognise the powerful feelings that these children evoke in us, the pain their predicament can provoke, and most of all, the limitations of what we can sometimes do. A well functioning team can be very helpful here: listening to each other's distress and clarifying issues. A team functioning poorly will often not recognise that it is mirroring the child or family psychopathology in its own process, and the despair is compounded. Main's classic paper describes this well.[17]

A second, related, way that the treatment can go wrong is in the therapeutic drift that comes from a unclear goals or a difficulty in appropriately placing children who cannot return to their families, at a time when social services resources are diminishing.

Thirdly the 'parental care' of the unit can fail under stress: demoralisation and disintegration of care set in, the emphasis switch from care and treatment to custodial control, and the fabric of the unit deteriorate. Here the stage is set for the excesses of institutional abuse that have recently been well publicised in residential environments. Prevention lies in good staff recruitment, and adequate leadership, supervision and support from experienced staff. There is no substitute for that human provision.

Finally inpatient units can sometimes be denigrated along with their patients, seen as places of 'last resort', and become over loaded with 'impossible' intractable problems. This obviously promotes demoralisation. The answer lies in patient selection, and a more active approach to the use of intensive treatment earlier in the course of psychopathology. The inpatient unit should not be seen as the end of the line, but rather an 'intensive therapy unit' where work can be undertaken at any stage in the development of psychiatric disorder.

How effective is inpatient treatment?

A number of studies have looked at the efficacy of inpatient treatment.[18–22] There have been great methodological problems in patient selection, comparison treatment groups, and the measurements of outcome, and there has not yet been a prospective randomised study of inpatient compared with community care for a particular disorder, although one is now being planned in the UK. In general, studies show beneficial treatment effects, particularly (hardly a surprise) with less severe disorders, and when there is specialised treatment programming and good aftercare. One provocative finding suggests that the length of admission has only a modest relationship to outcome.[20] This kind of result has led to suggestions of standard admission lengths for all patients.[13] This is rigid, and many severely damaged children undoubtedly benefit from longer admissions, but cost/benefit analysis for longer stays is bound to become an increasing concern.

Conclusions

The child psychiatry team has little in the way of technology to fall back on to effect cures. Medication has its place, but by and large the efficacy of our treatment relies on a psychological momentum generated and sustained within the staff group, the group of children and their families. The power, but also sometimes the weakness, of inpatient treatment lies in the size and intensity of this group process. Like any treatment it has drawbacks, but if these are recognised and the treatment prescribed appropriately, it can work powerful change. For obvious reasons the unit is an excellent source of training and teaching (at any one time the Booth Hall unit is training five psychiatric social work students, one psychology student, four training psychiatrists, and several learning nurses). It is potentially an excellent environment for the development and evaluation of new treatments and for scientific research; particularly, it is a place where children's behaviour can be precisely observed, as part of assessment and during treatment. Prospering in the future will depend on sensitivity to changing needs in referrers, and the recognition of the superiority of this mode of assessment and treatment, in some situations, over less intensive home oriented treatments. At its best a well functioning inpatient unit can have an effect on child mental health in a region which is considerably beyond the actual number of children who pass through it. Partly this will occur through research and training, but there is also an indefinable sense of it 'being there' as a resource and support for other professionals.

It is a pleasure to acknowledge that most of the ideas and practices described here were developed in collaboration with members of the inpatient team at Booth Hall Hospital.

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CURRENT TOPIC

Liver transplantation

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Orthotopic liver transplantation (OLT) is a therapeutic option that should be considered at an early stage in any child with a life threatening liver disease.[1] The majority of recipients can expect to enjoy a good quality life with normal growth and development.[2] Liver transplantation should be performed before growth is retarded by liver disease.[3] The results are better, however, in children transplanted after 1 year of age or when weighing more than 10 kg.[3 4] The procedure is best done electively rather than as an emergency.[5]

Since the National Institutes of Health Consensus Development Conference concluded in 1983 that liver transplantation was an effective therapy for end stage liver disease,[6] liver transplantation has gradually become available to more and more children. Over 1000 children had received liver grafts in the USA by 1990,[5] while by 1992 over 500 livers have been grafted into children aged less than 13 years in Europe; 50% were less than 3 years of age. Over 270 children, aged 16 or less, were transplanted by January 1992 in three British centres. Since 1983 the immediate outcome from transplantation has gradually improved because of developments in operative techniques, intensive care, immunosuppression, better prevention and control of infection, and earlier retransplantation when the first graft fails.[5 7] In the Cambridge/King's College Hospital liver transplantation programme, analysis of the first 100 children transplanted between December 1983 and March 1990[8] gave an overall survival rate of 65% but in the last two years the one year survival rate was 86%; five year survival rates ranging from 64 to 78% have been reported.[3 5 7] Even in infants under 12 months of age, one year survival figures of 65% have been achieved, although with considerable morbidity.[4] The use of reduction hepatectomy, in which a part of the right or left lobe from an older child or even an adult is used to replace the diseased liver, has decreased the chances of death while waiting for a donor of similar size and blood group.[9] In North America segmental grafts from living relatives have had a similar effect and given survival rates of 90% in infants in whom portoenterostomy for biliary atresia had been unsuccessful.[10]

Constraints

There are certain limitations which curb the use of this powerful therapy. Even in the best circumstances between 10% and 15% die within three months of grafting.[3 5 7–9] Removing and replacing a diseased liver is a demanding surgical procedure. The bile duct, hepatic artery, portal vein and hepatic veins, or inferior vena cava, require careful anastomosis to the appropriate host structures. Even more skill is required if only part of a liver is used.[9] A period of intensive care follows during which potentially lethal complications are common.[8 11–13]

Immunosuppression is achieved with cyclosporin, azathioprine and corticosteroids, the latter in relatively large doses initially when rejection is most severe. In the early weeks there is a very slender margin of safety between giving too much immunosuppresive therapy with an enhanced risk of infection and other toxic effects and giving too little and incurring rejection. Distinguishing acute rejection, which requires increased doses of corticosteroids and/or anti-lymphocytic antibodies, from systemic infection (viral, bacterial, fungal and/or protozoal) and from major complications requiring surgical management such as bile duct obstruction, hepatic artery thrombosis and/or portal vein thrombosis, is a major challenge. Preventing chronic rejection which is heralded by an insidious deterioration of liver function is another major difficulty. A new immunosuppressant, FK506, which promises to reduce the risk of both acute and chronic rejection, is currently being evaluated.[14] Up to 40% of recipients require regrafting, mainly for chronic rejection, vascular thrombosis, or primary nonfunction.

The patient is at risk from longer term surgical complications, and medical problems associated with lifelong immunosuppression. Opportunistic infections and community acquired infections are always a danger.[15] A worrying complication is Epstein-Barr virus related lymphoproliferative disease, which is frequently fatal unless immunosuppressive drugs are stopped. In one paediatric series an incidence of over 2·8% per year was reported.[16] Deaths are rare between two and five years after OLT. The longer term prognosis remains unknown. The longest surviving recipient remains well more than 20 years after transplantation.[5]

Lack of donor livers matched for size, blood group, and cytomegalovirus (CMV) status remains a major difficulty particularly in those less than 2 years of age. Surgical advances including reduction hepatectomy and split liver grafting have helped, but have increased complication rates in the short term at least.[3 5] Another important limiting factor is scarcity of intensive care facilities and trained nursing staff.

Indications for liver transplantation and its timing

Initially OLT was undertaken mainly in children with chronic liver disease, but OLT now has an increasingly effective role in the management of selected children with fulminant liver failure. It has also been successful in some liver based metabolic disorders, in which liver function and structure are not primarily affected but in which irreparable damage to other vital organs can occur (table 1). Rarely it has been used for children with cholestatic disorders in whom the quality of life is severely impaired by pruritus or osteopenia, although liver damage is not advanced. It has a limited role in liver tumours which cannot be successfully treated by subtotal hepatectomy and cytotoxics.

The timing of liver transplantation is determined by consideration of the child's prospects with other forms of treatment, the anticipated availability of a donor and of transplant facilities, and the likely outcome of OLT. It is essential to confirm the primary diagnosis of the liver disease, to estimate its severity, and to be aware of its likely evolution with other forms of treatment. Comprehensive evaluation is essential in minimising adverse effects of the procedure on the child and family. The transplantation coordinator, nutritionist, psychologist, nurse specialist, and social worker are indispensable in this process.[17 18]

CHRONIC LIVER DISORDERS

Selecting the best time for surgery is difficult. A major problem in any form of cirrhosis is that the course may be punctuated by life threatening complications. If these are anticipated and treated effectively the child may remain well with normal growth and development for many years. If mismanaged the patient may die prematurely. Complications which warn that early assessment for transplantation is essential in any form of chronic liver disease are given in table 2. In particular disorders other features are of prognostic importance. If jaundice persists after portoenterostomy for biliary atresia, transplantation is indicated as soon as linear growth slows or at the earliest signs of complications of cirrhosis. Recurrence of jaundice in patients with α_1-antitrypsin deficiency (protease inhibitor phenotype ZZ) requires similarly urgent action.[20] Wilson's disease is fatal without transplantation in those presenting with fulminant liver failure and in 50% of those with cirrhosis. For those with cirrhosis a useful index distinguishes children who should be transplanted as soon as a donor becomes available from those who will survive with penicillamine therapy alone or with zinc sulphate.[21]

Table 1 Liver transplantation for metabolic disorders

End stage liver disease or premalignant changes
- α_1-Antitrypsin deficiency
- Wilson's disease
- Tyrosinaemia
- Galactosaemia
- Haemochromatosis
- Glycogen storage disease type 4
- Cystic fibrosis
- Defects of fatty acid oxidation
- Glycogen storage disease type 1

For major extrahepatic features
- Familial hypercholesterolaemia
- Primary hyperoxaluria
- Crigler–Najjar syndrome
- Factor VIII deficiency
- Protein C deficiency
- Tyrosinaemia
- Urea cycle defects
- Glycogen storage disease type 1

Table 2 Indications for liver transplantation in chronic liver disease

Ascites refractory to fluid restriction and diuretics
Alimentary bleeding not controlled by sclerotherapy or propranolol
Spontaneous bacterial peritonitis
Growth retardation
Hepatic encephalopathy
Hypoxia
Prothrombin ratio (INR) >1·4
Cholesterol <2·6 mmol/l (100 mg/100 ml)
Indirect bilirubin >102 μmol/l (6 mg/100 ml)
Poor MEGEX test result[19]

In the acute form of tyrosinaemia liver transplantation should be performed as soon as growth arrest occurs, usually around 5 months of age. For the more chronic form it should be undertaken if the metabolic complications cannot be controlled by diet and drug treatment or at the earliest suspicion of malignant change within the liver. By 3 years of age the risk of hepatocellular carcinoma is so high that elective transplantation must be considered if the liver is nodular on ultrasonic or computed tomographic scans.[22]

The results of liver transplantation in over 30 patients with cystic fibrosis with predominantly liver involvement appear to be as good as in other disorders with as yet no evidence that infective complications other than pseudomonas and aspergillosis are particular problems. Some recipients experience a significant improvement in pulmonary function.[5]

Although a rational plan can be developed for most children with chronic liver disease on the basis of current knowledge, a more sound scientific basis for estimating the risks with or without transplantation in the individual patient would be invaluable. Paediatric hepatology units in conjunction with referring paediatricians must develop a database which would allow more precise determination of the exact indications for transplantation. Referral as soon as the patient is identified as having a liver disorder requiring possible transplantation will help to achieve this. Equally important, early referral may assist by confirming the exact diagnosis, suggesting alternative treatment and help in managing complications.

ACUTE LIVER FAILURE

Although acute liver failure is potentially reversible with full recovery, the mortality without transplantation is 90% if the international normalised prothrombin ratio (INR) is greater than 4·0 rising to 100% if over 6. The complications of this multisystem disorder, particularly cerebral oedema, renal failure and systemic infection, require meticulous intensive care and a ready supply of donors if transplantation is to be successful. Four of seven children with severe acute liver failure (INR> 4) transplanted between March 1988 and August 1991 at King's

College Hospital survive with a median follow up of 18 months.[23] Therefore any child with apparent acute liver disease and encephalopathy, or with an INR prothrombin ratio of greater than 1·6 which is not corrected by intravenous vitamin K, should be referred to a unit offering skilled intensive care and the possibility of early transplantation if indicated.

LIVER BASED METABOLIC DISORDERS

In liver based metabolic disorders associated with liver damage the indications for transplantation (table 1) are similar to those in any other form of cirrhosis except where mentioned in the text. The current indications for transplantation when the liver is structurally normal but the patient is at risk from irreparable damage to vital tissue (for example, the brain, heart, or kidneys), caused by a hepatic based defect in metabolism, has been the subject of recent reviews.[24 25] In two rapidly developing fields close liaison between hepatologists and specialists in metabolic disorders is mandatory. OLT has not been effective in erythropoietic protoporphyria and Niemann–Pick disease type II.

Contraindications

Contraindications for transplantation are in a state of flux as surgical and medical advances overcome particular problems. At present metastatic malignancy, intractable extrahepatic sepsis particularly fungal, and permanent neurological damage are considered contraindications. Relative contraindications include complex congenital heart disease, major intra-abdominal vascular anomalies, advanced renal or lung disease, and severe short bowel syndrome. The place of transplantation in patients with cirrhosis due to hepatitis B is controversial since the recurrence of viral infection, with a high incidence liver damage, cannot be reliably prevented. Its onset can be delayed by hyperimmune gammaglobulin. The position of liver transplantation in the patient who is positive for HIV is even more contentious.[5 7]

Improving the outcome of liver transplantation

The primary paediatrician can work with the hepatologist in minimising complications. Before transplantation a full programme of immunisation against viruses, *Streptococcus pneumoniae*, and *Haemophilus influenzae* should be instituted. Avoiding unnecessary hospitalisation and/or antimicrobials before transplantation will reduce the risk of colonisation by resistant organisms. Expert care of complications of cirrhosis such as bleeding varices and ascites will help to bring the patient to transplantation in better condition and minimise postoperative problems. Nutritional support in the form of calories, protein and vitamin supplements if necessary, given by nasogastric feeding and rarely intravenously, may allow the patient to tolerate transplantation more satisfactorily.[3 17] Every effort should be made to avoid intra-abdominal surgery in patients who are potential candidates. Surgery in the area of the porta hepatis causes particular difficulties. The parents, and as far as possible the child, should be fully informed of the likely course and possible problems so that they and the family can make the appropriate plans.

The remarkable wellbeing, restored energy, catch-up growth, good scholastic performance and social adjustment of survivors, many of whom were desperately ill while awaiting transplantation, should be a stimulus to further developments to bring the early mortality of this procedure down to that of more conventional surgical procedures. With the present rate of improvements in surgical techniques, donor organ preservation, immunosuppression, antimicrobial measures and supportive care, this seems a realistic goal in the next decade. For this to become possible in Britain or northern Europe it will be essential to expand intensive care facilities for children.

Paediatricians have a key role in the early recognition and referral of infants and children with life threatening acute and chronic liver disorders. With early referral, less hazardous treatment may be possible. Biliary atresia accounts for 50–70% of children transplanted in most centres.[3–5 8] In up to 70% of children portoenterostomy before 8 weeks of age delayed transplantation for up to 15 years, if not indefinitely.[26] The majority in Britian are still receiving surgery after 8 weeks of age because primary physicians and paediatricians fail to recognise that significant hepatobiliary disease is always present in any child with even a mild conjugated jaundice.[27] Early referral can be equally efficacious in other disorders. It also gives more time to minimise potential complications and gives a greater chance of finding a suitable donor. Scarcity of donors is still a major obstacle to optimising this therapy in infants and young children. Paediatricians and workers in the intensive care facilities must recognise that organ donation is a potentially positive step for some donors' families as well as being life saving for the recipient.

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Occult liver injury in child abuse

Abdominal injury in child abuse may be more common than is generally realised. Over a nine month period in 1989–90 doctors at the Children's Hospital in Buffalo, New York State (Pierre N Coant and colleagues, *Pediatrics* 1992;**89**:274–8) examined 50 children suspected of physical (non-sexual) abuse. One had clinical evidence of abdominal trauma but the remaining 49 had no suggestion of abdominal injury either from the history or on clinical examination. Serum activities of liver enzymes (aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase (LDH) were measured routinely and four of the 49 children had raised activities usually of all three enzymes, although in one patient only the AST was high. The four children with raised enzymes each had an abdominal computed tomogram and three of them were shown to have lacerations of the liver. All of them recovered without surgery. The enzyme activities returned to normal within 48 hours and the degree of increase was very variable (between twice and 100 times the upper limit of normal) possibly because of variation in the time from injury to presentation at the hospital.

Though these children recovered without treatment, it is clearly important to know about these injuries because not only do the children need careful observation to ensure that they recover without complication but the injuries are of themselves of great legal significance and the knowledge is important in planning future management. Most children with physical injuries suspected to be non-accidental have blood taken for a blood count and clotting screen; it seems reasonable to include a transaminase activity at the same time. The incidence of liver laceration in this series was 6% but some of the children (the authors do not say how many) did not suffer physical trauma but were examined because of suspicion. In children with definite physical injuries the incidence of liver trauma would presumably be higher.

It is interesting that the liver lacerations in this series were all to the left of the liver whereas accidental injury to the liver usually involves the right side. Clearly a right handed blow is likely to strike the left side of the liver if delivered from the front. Similarly splenic injury is said to be rare in child abuse, presumably because the spleen is protected by the rib cage from a right handed blow. The handedness of the alleged assailant might also be of legal significance.

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CURRENT TOPIC

Hearing impairment after bacterial meningitis: a review

H M Fortnum

Postmeningitic hearing impairment is an important public health problem with implications for both paediatric and audiology services. A recent population study has shown that, by the age of 3 years, the proportion of children with a known bilateral profound hearing impairment who have an *acquired* impairment is approximately 20%. Of these acquired impairments, 90% are probably due to bacterial meningitis.[1] Furthermore, studies of cohorts of children born in the 1970s and early 1980s indicate that 6% of all childhood hearing impairment is due to bacterial meningitis.[2 3]

Not all children surviving bacterial meningitis suffer permanent sensorineural hearing impairment. How many do, and why are certain children affected but not others? Are there any factors within the illness, within the children, or within the medical treatment that could predict the children at greatest risk? This article reviews the recent literature as a source of answers to these questions and recommends management guidelines in the light of current knowledge of the pathology. (Except where otherwise stated, 'impairment' in this article refers to *sensorineural* hearing impairment, that is permanently raised hearing thresholds and loss of other auditory functions such as frequency resolution, due to damage to the eighth nerve or to the receptor cells of the inner ear.)

Total loss of hearing disrupts the development of communication skills, particularly in young children who have not fully developed speech and language. It can also lead to regression to an earlier stage.[4] This disruption is an important sequela of bacterial meningitis, justifying the effort of early identification to enable appropriate habilitation to begin as soon as possible. Partial hearing impairment and/or unilateral losses also occur[5–10] and also need to be identified with minimal delay, because these children may also suffer auditory and linguistic disabilities that are only subtly symptomatic. Such children often display behavioural compensations and may appear to hear normally. Unaware of what he is missing, a young child will not complain. Crucial stimulation may be missed,[11] which is particularly important at school entry. Parents and teachers should be aware of any degree of impairment, even if it is too mild for hearing aids to be beneficial.

Bacterial meningitis may also cause more widespread damage. If a child is left with multiple handicaps, any hearing impairment is more easily overlooked and difficult to detect. In such children assisting any impairment to hearing may be of even greater benefit than in less complex cases.

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What is the incidence of postmeningitic hearing impairment?

From a review of the recent literature, the incidence of hearing impairment in children surviving bacterial meningitis may be as low as 3·5%[12] or as high as 37·2%.[13] The 10-fold range certainly reflects the large sampling errors associated with small samples, but probably also reflects some bias due to case selection and methodology, for example, the type and severity of the hearing impairment included, the timing of assessment after the onset of the illness, the age range of the children, the profile of infecting organisms, and the sophistication of the audiological tests used. Table 1 summarises the recent literature and includes only those studies considered to provide the most trustworthy estimates. The criteria for inclusion of a study were (a) publication in 1977 or later (that is in the last 15 years), (b) sample size over 50 in a consecutive series, (c) a well defined age group including children up to at least 3 years of age, (d) the use of age appropriate audiological testing methods, and (e) audiological testing of more than 80% of the original cases. From the selected papers an overall rate and confidence intervals were computed (weighted by the number of cases in each study) for permanent sensorineural hearing impairment of any degree among survivors of bacterial meningitis. Table 2 gives the results of these calculations for all causes of the illness and for each of the three main infective agents. This synthesis gives an incidence of 9·6%.[8 10 14–20] Interpreting the computed confidence intervals, the risk of permanent sensorineural hearing impairment lies between one in 12 and one in eight. This compares with the risk in the background childhood population (<3 years) of approximately one in 600 for any degree of permanent sensorineural hearing loss. Thus the raised relative risk is 50- to 75-fold. However, in countries other than those studied, mainly North America and north west Europe, the contribution of each of the infecting organisms is very different and caution must be used in interpreting and generalising these figures.

For bilateral profound or total impairment the range in reported incidence is between 1% and 4%.[8–10 14 16–18 21–23] Projected on to an incidence of bacterial meningitis of about 0·3 per 1000 per year aged 0 to 14 years and a mortality rate of approximately 10% (H M

Table 1 Incidence of sensorineural hearing impairment after bacterial meningitis

Author(s)	*Study date*	*Place*	*Age*	*No tested*	*Organism*	*Incidence of SNHI of any degree (%)*	*Incidence of profound bilateral SNHI (%)*
Salwen *et al*[14]	1956–80	Sweden	1 month–16 years	181	All	11·6	3·9
				115	*H influenzae*	9·6	—
				51	Meningococcus	10	—
				15	Pneumococcus	33	—
Koskiniemi *et al*[53]	1960–74	Finland	2 months–9 years	101	*H influenzae*	13·9 (>moderate)	—
Rosenhall *et al*[9]	1968–75	Sweden	0–22 years	83	*H influenzae*	18·1	3·6 (bilateral >70 dB)
Moss[54]	1971–74	UK	1 month–8 years	60	Meningococcus	5·0	
Claesson *et al*[21]	1971–80	Sweden	0–15 years	128	*H influenzae*	14·8	1·4
Pomeroy *et al*[15]	1973–77	USA	1 month–14 years	185	All	9·7	7·2 (bilateral >80 dB)
Dodge *et al*[10]	1973–77	USA	2 months–14 years	185	All	10·3	2·2
				118	*H influenzae*	5·9	1·7
				19	Meningococcus	10·5	0
				29	Pneumococcus	31	6·9
				19	Other	5·3	0
Dawson *et al*[16]	1975–87	New Zealand	1 month–13 years	143	All	6·3	3·5
				99	*H influenzae*	—	2
				24	Pneumococcus	—	12·5
Richner *et al*[30]	to 1977	Switzerland	3 months–8 years	97	*H influenzae*	15·5	—
Edwards and Baker[31]	1977–79	USA	0–16 years	79	Meningococcus	6·3	0
Guiscafre *et al*[17]	1978–79	Mexico	1 week–15 years	100	All	8	1 (bilateral >70 dB)
				30	*H influenzae*	6·7	—
				18	Other	22·2	—
				52	Not known	3·8	—
Ozdamer *et al*[18]	1978–81	USA	3 weeks–3·5 years	60	All	11·7	3·3
				46	*H influenzae*	6·5	—
				8	Pneumococcus	50	—
Vienny *et al*[8]	1979–82	Switzerland	1 week–16 years	51	All	9·8	2
Cartwright *et al*[22]	1981–86	UK	0–24 years	63	Meningococcus	9·5	3·2
Smith *et al*[23]	1982–83	West Africa	0–14 years	126	Meningococcus	7·1	2·4
Lebel *et al*[19]	1984–85	USA	2 months–16 years	176	All	9·1	—
				137	*H influenzae*	9·5	—
				14	Pneumococcus	21·4	—
				25	Other	0	—
Odio *et al*[20]	1990	Costa Rica	6 weeks–13 years	94	All	10·6	—

All, all bacteria; SNHI, sensorineural hearing impairment.

Table 2 Overall rate for incidence of permanent sensorineural hearing impairment after bacterial meningitis as computed from studies included in table 1

Type of meningitis	*Study reference number*	*No in study*	*No hearing impaired*	*Estimate (%)*	*Range of studies (%)*	*Computed weighted confidence intervals (%)*
Unselected	8, 10, 14, 16, 17, 18, 19, 20	1175	113	9·6	6·3–11·7	7·9 to 11·3
H influenzae	9, 10, 14, 17, 18, 19, 21, 30, 53	871	99	11·4	5·9–18·1	9·3 to 13·5
Meningococcal	10, 14, 22, 23, 31, 54	398	30	7·5	5·0–10·5	5·0 to 10·1
Pneumococcal	10, 14, 18, 19	66	21	31·8	21·4–50·0	20·7 to 42·8

Fortnum, A Davis, and P Ispahani, in preparation), this would amount to 60 or 70 profoundly impaired children each year in England, Scotland, and Wales.

Table 3 Risk factors for hearing impairment from various studies (study reference numbers given)

Clinical measure	*Significantly raised risk of hearing impairment*	*No raised risk of hearing impairment*
Factors within the illness:		
Low CSF glucose	5, 8, 10, 19, 24, 25, 26	18, 31
Increased CSF protein		5, 8, 10, 19, 25, 29, 30, 31
Increased CSF white cell count	5, 31	8, 10, 19, 25, 29, 30
Ataxia or vestibular disturbance	20, 27, 28	10
Severe neurological deficits	5, 10	18, 30
Organism:		29, 35
Meningococcus	5 (>2·5 years)	
Pneumococcus	18	
Coincident middle ear disease		5, 18
Hospital >14 days	18	
Seizures	26	10, 14, 18, 35
Hydrocephalus		18
Subdural effusions		10, 18, 53
CSF pressure		5
Factors within the child:		
Age		5, 10, 18, 29, 30
Sex		5, 10, 18
Factors within the treatment:		
More time from symptoms to treatment	5, 14, 30, 55	8, 10, 18
No steroid treatment compared with steroid treatment	19, 48 (*S pneumoniae*)	20, 48 (meningococcus and *H influenzae*)
Partial antibiotic treatment		25
Delayed CSF sterilisation	56	

CSF, cerebrospinal fluid.

Can any factors predict hearing impairment?

Table 3 lists several factors which have been studied in sufficient numbers of children to give quantitatively stable results, and lists those studies which found an association with the various factors and those which did not. All of these studies are, inevitably, descriptive with data derived from clinical judgments. In terms of the quality of evidence presented, only one of the quoted papers reports relative risk values with confidence intervals.[20]

CLINICAL SIGNS

For those studies that measured it, an initial low concentration of glucose in the cerebrospinal fluid almost universally carried a much raised risk of hearing impairment.[5 8 10 19 24–26] The three studies that reported values gave a statistically significant raised risk at concentrations of <0·6 mmol/l,[25] <1·1 mmol/l,[10] and <2·15 mmol/l.[8] The presence of ataxia or vestibular disturbance also indicates a child at a higher risk of hearing impairment.[20 27 28] However, this is likely to be a correlated effect rather than a useful causal predictor and is, anyway, difficult to recognise in very young, very sick infants.

Most studies agree that a raised cerebrospinal fluid white cell count[8 10 19 25 29 30] or a raised cerebrospinal fluid protein concentration[5 8 10 19 25 29–31] is not predictive of hearing impairment.

CAUSATIVE ORGANISM

Different risks have been reported from different organisms,[5 18] particularly a higher risk of hearing impairment after infection with *Streptococcus pneumoniae*. Where a study has reported differences between organisms this is shown in table 1 and the overall computed incidence rates are shown in table 2. For *Haemophilus influenzae* and meningococcal infections these rates are reliable estimates. The numbers for pneumococcal infections are small and are hence the most open to any selection bias that might have a large effect on the rate, so the apparently higher contingent incidence should be viewed with caution. Permanent sensorineural hearing impairment is not truly organism specific, having been documented for almost all possible causes of bacterial meningitis. There have also been a few documented cases of hearing impairment after viral meningitis,[13 17] but there has been no comprehensive epidemiological study of this and further research is needed.

AGE

Bacterial meningitis has been documented in children of all ages from neonates to 16 years.[5 8 10 13] It does occur beyond infancy, although the greater vulnerability of very young children to more severe infections may result in a higher proportion of them suffering sequelae of all forms. The fact that some studies have restricted their population by age may explain some of the differences in incidence figures reported in table 1.

In summary, the evidence to date on risk factors indicates that hearing impairment cannot be exclusively predicted by a small number of risk factors. It should be assumed to be a possibility in every case until proved otherwise by thorough audiological testing.

How is the damage mediated?

Hearing impairment after meningitis may have several different causes. Most likely is the effect of suppurative labyrinthitis, due to direct spread of the infection from the subarachnoid space through the cochlear aqueduct.[5 6 10 32 33] This leads to destruction of sensory structures and no recovery of hearing. On the other hand, a toxic or serous labyrinthitis is thought to be the mechanism responsible for partial and reversible losses.[5 32 34] Other possible mechanisms include direct nerve fibre damage[8 14 35] and secondary ischaemic damage.[6 8 19 35]

Recent studies of experimental animal models have provided more details of the possible mechanism of the damage.[36 37] These studies have shown that lysis of bacterial cells by antimicrobial agents produces endotoxin from Gram negative bacteria and lipoteichoic acid from Gram positive bacteria. These lead to the release of cytokines such as tumour necrosis factor and interleukin-1 which initiate a generalised inflammatory response. This inflammation may be responsible for the hair cell damage in the inner ear observed in experimentally infected animals.[36] Roos provides a good review of recent work.[38]

Is the impairment permanent and stable?

The permanence and stability of hearing impairment after bacterial meningitis are important for at least two reasons. Firstly, for the profoundly impaired child one option for rehabilitation now available is a cochlear implant. Postmeningitic children, who have been deafened perilingually or postlingually, are a highly successful group of implantees.[39] Implantation involves insertion of a single or multichannel electrode through the round window into the cochlea with the aim of stimulating the sensory nerve endings. In implantation there is potential risk of destruction of the receptor cells directly or via rupture of membranes separating fluids of different ionic content, leading both to poisoning of the cells and disruption of the primary hydromechanical and chemical properties of the cochlea. If aidable hearing is present, or is likely to return, this procedure is obviously not in the best interests of the child. Thus, any evidence that profound hearing losses may not be permanent has important implications. Rosenhall and Kankkunen report three cases of improvement from bilateral profound losses over periods of 18 months, 4·5 years, and 6 years.[34] However, improvements in hearing after meningitis have more often been reported among cases with less severe hearing losses.[5 6 8 17] Reports of complete or partial recovery may be due to improvements in the accuracy of testing as the child gets older or to resolution of simultaneously present conductive hearing losses due to fluid in the middle ear,[7 10 13 40] particularly if the first measurement is soon after the infection.

Secondly, any instability in hearing impairment is important as a potential obstacle to a child's development of communication skills. It also has implications for the resources needed in continued follow up of such children. Fluctuations have been documented, again notably by Rosenhall and Kankkunen.[41] Their explanation was a form of endolymphatic hydrops caused by suppurative labyrinthitis. Alternatively, these children may have had coincident middle ear conductive problems.[40] Underlying sensorineural impairments probably do not fluctuate. A few cases of a deterioration in threshold levels between 5 and 12 years after the episode of meningitis have been noted,[6 42] but attributing these losses solely to the meningitis is questionable.

Can we reduce the risk?

There have been recent advances in both the prevention and treatment of bacterial meningitis. The potential value of immunisation has been acknowledged and researched for many years[43 44] and in October 1992 immunisation for *H influenzae* infections will become a reality in the UK. The new *H influenzae* b vaccine, given to children at the time of the standard triple vaccine (diphtheria, pertussis, and tetanus) is intended to prevent the majority of cases. An estimate of the potential health gain may be made by projecting the optimistic assumptions of 100% uptake and 100% effectiveness onto figures from a recent 10 year retrospective study (H M Fortnum, A Davis and P Ispahani, in preparation) in Nottingham District Health Authority (1989: total child population 0 to 14 years=113603, 18% of all age total). Such a vaccine given at 3 months of age might have prevented 78 cases of meningitis over 10 years including one death and three cases of permanent sensorineural hearing impairment (one profound bilateral and two severe to profound unilateral). It would not have prevented six cases in children aged less than 4 months, two of whom died. Projecting these figures on to the population of England, Scotland, and Wales, a vaccine might prevent up to 700 cases of meningitis due to *H influenzae* per year. Applying the overall incidence rate from table 2 would predict a consequent reduction of 65 to 95 children per year with permanent hearing loss but these figures may not truly represent the UK population in the 1990s and should be used with caution.

The role of factors within treatment is uncertain. In the past the discussion has mainly concentrated on the question of appropriate antibiotics[45 46] and delay to treatment. Well conducted studies have found both for and against an increased risk if treatment is delayed more than 48 hours (table 3). It is likely that this conflicting evidence is the result of the involvement of other factors, as it is generally accepted that any damage to hearing occurs early in the infection.[6 10 17 24 47] More recently, in the search for effective treatment, steroids have received much attention. If given at the same time as antibiotics, dexamethasone lessens the inflammatory response[37] and may block much of the cochlear damage.[36] Three studies reported a lesser risk of neurological sequelae in steroid-treated children,[19 20 48] but only two of the three found a lesser risk of hearing impairment.[19 48] Other studies have reported benefit from the use of non-steroidal anti-inflammatory agents,[49 50] but more and larger studies are needed to determine the true benefits and costs of introducing anti-inflammatory drugs as routine treatment.

Recommendations

All children recovering from bacterial meningitis should be referred for audiological assessment before discharge from hospital.[51] For administrative and motivational reasons immediate cross referrals are more likely than later ones to result in an appointment actually being made. The appointment should take place about four to six weeks later. If a child is seen too early an associated conductive loss may be identified, requiring further follow up before the possibility of an underlying sensorineural impairment can be discounted. However, if the appointment is made later the impact of the acute life threatening disease on the parents may have lessened and they may not think it important enough to bring the child for the appointment. In this way a significant degree of hearing impairment could go undetected until the child meets a circumstance where unimpaired auditory input becomes a higher priority (for example at school entry). Also a non-attended appointment at a specialist centre is a waste of scarce resources.

Another reason for minimising the delay to referral, and therefore to assessment and identification of any hearing impairment, is the process of ossification of the cochlea that can occur within a few months of meningitis. This process is important in profound hearing losses because if ossification has progressed too far an intracochlear implant becomes surgically very difficult to insert[52] and extracochlear implants confer less benefit.[39] Thus the window of four to six weeks reconciles the increased resource implications of referral too early with the dangers of referral too late.

The professional responsibility for initiating referral of the child for hearing assessment has to lie with the paediatrician responsible for the child in hospital. It is an obligation of the paediatric service to ensure that a fail-safe administrative system exists to make certain that referral actually occurs. Any subsequent non-attendance should be followed up with close cooperation between the general paediatric and audiology services.

Assessment of the hearing of young children is not easy. It requires great skill and patience particularly to detect mild or unilateral impairments and particularly in younger children. Conventional pure tone audiometry can be reliably used in children over the age of 3 or 4 years with minimal modification, but 80% of bacterial meningitis occurs before age 3. Accurate testing of younger children is possible if the relevant skills are available. Usually this will require referral to a subregional or regional centre specialising in paediatric audiology. Stressing the importance of the potential problem to the parents will help to ensure attendance. On no account should the child's hearing be tested by informal and imprecise methods in an outpatient clinic or at the bedside, as this could give an incorrect result and a false sense of security. Neonates and very young infants should have their hearing assessed with brainstem auditory evoked potentials.

This article has concentrated on bacterial meningitis but the question often arises of the possibility of hearing impairment after viral meningitis. This is a more difficult link to study but until further research proves otherwise, any child with encephalitis, or ill enough with viral meningitis to merit hospital admission, should also have a formal assessment of hearing after discharge. This should also apply to any child with viral meningitis treated outside hospital, even some time before, where there is concern over hearing, speech or balance. There will also be children known to have had meningitis before the introduction of fail-safe mechanisms of referral. If concern is expressed over the hearing or speech of such children, the possibility of meningitic damage should be considered and referral made for audiological assessment to exclude this cause before other aetiologies are sought.

Summary

The recent literature reports the incidence of permanent sensorineural hearing impairment in children surviving bacterial meningitis to be approximately 10%. The question of why some children surviving bacterial meningitis suffer a hearing impairment while others recover completely remains unanswered. Very few of the factors so far studied have any predictive power. Knowledge of those that do, for example low concentrations of cerebrospinal fluid glucose, may improve our understanding of the pathological mechanisms involved and ultimately possibly lead to methods of prevention, but at present do not allow useful prediction of those who will be affected.

The role of steroids and non-steroidal anti-inflammatory agents needs further investigation. These may yet prove to be useful interventions to prevent mortality and morbidity caused by bacterial meningitis. The best hope of preventing serious sequelae of bacterial meningitis is primary prevention and currently vaccination offers the most promising solution. Further research will no doubt expand the range of causative organisms covered. Up to date epidemiological studies of the UK population are needed to enable an accurate assessment of the extent of the problem and the potential health gain from advances in prevention or treatment.

Children will continue to suffer bacterial meningitis. Most will survive but some of them will be left with impaired hearing. Such children must be identified as quickly as possible to enable timely secondary prevention of disability or handicap.

My thanks go to Professor Mark Haggard, Professor David Hull, Dr Adrian Davis, and Dr Michael Tarlow for constructive comments on an earlier draft of this paper.

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Turning off the bilirubin tap

If there's too much water in your bucket you can syphon it off, enlarge the hole in the bucket, make new holes, or turn off the tap. Treatment of hyperbilirubinaemia has been aimed at syphoning (exchange transfusion), enlarging the hole (enzyme induction), or creating new holes (phototherapy) but little attention has been paid to the possibility of turning off the tap, although some children have been given a new bucket.

In the production of bilirubin from haem the rate-limiting enzyme is haem oxygenase and this enzyme is inhibited by tin-containing porphyrin molecules which act as competitive, non-metabolised inhibitors. Tin protoporphyrin is one such molecule but tin mesoporphyrin is apparently more potent.

A report from the Rockefeller University Hospital in New York (Richard A Galbraith and colleagues, *Pediatrics* 1992;**89**:175–82) describes the effect of giving tin mesoporphyrin to two 17 year olds with Crigler-Najjar disease type I. The study was complex and difficult to interpret because phototherapy and repeated plasmapheresis were continued at the same time and patients were estimated to have a very large tissue load of bilirubin. Nevertheless there seemed to be some effect from the tin mesoporphyrin in so far as mean serum bilirubin concentrations were lower during this treatment and the rebound increase in serum bilirubin after plasmapheresis was slower. Both of the patients had shown recent neurological deterioration, which appeared not to progress during the treatment.

These studies seem to be of more theoretical than practical interest. Long term treatment with phototherapy has been practised in Crigler-Najjar disease for at least 20 years. It is very difficult to maintain, home phototherapy being fraught with severe practical and psychological problems, and neurological deterioration during the teenage years has been described by several authors. Liver transplantation in childhood has been performed in various centres on patients with this disease and currently seems to be the most attractive option. A major drawback of the haem oxygenase inhibitors is severe photosensitisation, although otherwise they seem to be non-toxic.

The idea of turning off the bilirubin tap seems an attractive one but at present its application seems likely to be very limited in practice.

ARCHIVIST

LETTERS TO THE EDITOR

Desmopressin for bedwetting

SIR,—The article by Evans and Meadow cast further light on the ongoing controversy over the causes of nocturnal enuresis in children.[1] While some stress the importance of small bladder capacity[2] and others the importance of nocturnal polyuria caused by deficient arginine vasopressin (AVP) secretion,[3] many take the compromise of both factors playing their part.[4] In this paper, enuretics responsive to desmopressin had higher nocturnal volumes (345 ml) and lower nocturnal urinary AVP concentrations (0·9) compared with non-responders (265 and 2·8 respectively). While these differences were insignificant for the small numbers of children involved (eight and 10 respectively) the authors rightly point out that there did appear to be 'a trend towards desmopressin responsive enuretics having lower AVP concentrations and larger volumes of dilute urine at night'. It could well be that significant differences are found with larger numbers of children. It was also interesting that the age of desmopressin responders who appeared to produce more dilute urine was 12 compared with only 9 in the others. This supports our own feeling that the cause of nocturnal enuresis is more likely to be lack of nocturnal AVP secretion in older children and adults and smaller function bladder capacity in those younger. A lot of the work identifying nocturnal enuretics who are AVP deficient was done on older children and adults.[2 5] There was therefore no real support for Evans and Meadows suggestion that 'It is possible that the diurnal variations in AVP are less well developed in younger children'.

Recently we did a short study of nocturnal enuresis in 5 year olds to see if the enuretics produced more dilute urine overnight. At the routine medical on joining school, children were asked to bring along the first urine specimen of the day for measurement of osmolality. (This study was passed by our local ethics committee.) Fifty five children produced samples: 46 who were virtually dry and nine who wet the bed most nights. Mean (SD) osmolality of those who were dry was 801 (180) and of the enuretics 760 (264) mmol/kg (not significant). While it is possible that early morning osmolality may not be fully representative of total overnight urine production if the child has previously wet the bed, we feel this study does indicate that enuresis in young children is unlikely to be due to nocturnal polyuria. This type of developmental nocturnal enuresis is probably mainly due to low functional bladder capacity at night. In studies of nocturnal enuresis a firm distinction should be made between such children with developmental enuresis and older children and adults.

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1 Evans JHC, Meadow SR. Desmopressin for bed wetting: length of treatment, vasopressin secretion, and response. *Arch Dis Child* 1992;67: 184–8.
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SIR,—We read with interest the report by Evans and Meadow on use of intranasal desmopressin for bedwetting.[1] These authors did not find any statistically significant difference in nocturnal urine volume, osmolality, or arginine vasopressin (AVP) concentration between responders, non-responders, and controls. We believe that one explanation for the observed lack of statistical significance may be that these authors examined a heterogeneous group of patients. Evans and Meadow included patients with diurnal symptoms, behavioural problems, and adverse family or social factors. They also included children who were only intermittently enuretic. Only 15 of 28 children treated for one month and 17 of 27 treated for three months were dry ≤2 nights per week before treatment.

Evans and Meadow acknowledge the presence of a trend towards lower AVP concentrations and larger volumes of dilute urine in responders. We believe that statistical significance may have been achieved with either a larger group of patients or a more homogeneous patient population. Our experience suggests that desmopressin is most efficacious in children with primary nocturnal enuresis who do not have diurnal symptoms or possible adverse behavioural or social circumstances and who are consistently rather than intermittently wet at night.[2]

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1 Evans JHC, Meadow SR. Desmopressin for bed wetting: length of treatment, vasopressin secretion, and response. *Arch Dis Child* 1992;67: 184–8.
2 Robson WLM, Leung AKC. Children with primary nocturnal enuresis. *Contemporary Pediatrics* 1990;1:19–25.

Dr Evans comments:

Drs Morton and Daniels raise the interesting hypothesis that enuretic children can be divided into two groups: children who suffer from maternal polyuria secondary to vasopressin deficiency and younger children who have smaller function bladder capacities. Certainly our desmopressin responsive patients were older and other authors have made the same observation.[1] However such a clear cut distinction is unlikely in clinical practice as the majority of these older children will have been enuretic when younger. It seems unlikely that this group and the other secondary onset enuretic children would have the same underlying physiological abnormality.

Drs Robson and Leung find that desmopressin is most efficacious in children with primary nocturnal enuresis without diurnal symptoms or adverse behavioural or social circumstances. It is likely that most treatments for enuresis would be more effective in such a group of children. Their observation that children who have consistently rather than intermittently responded better is interesting and contrasts with our experience that children who wet the bed every night responded extremely poorly to desmopressin. In our experience on an unselected group of children attending a local enuresis clinic and in other authors' experience[2 3] desmopressin results in a minority of children becoming dry while on treatment and even fewer remaining dry when treatment is withdrawn.

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Comparison of BCG vaccination at birth and at third month of life

SIR,—I read with interest the paper by Ildirim *et al.*[1] The authors recommend that practice be changed in those countries in which BCG is given to newborn infants, and that the vaccine be given at the end of the third month instead. I would be concerned that the uptake and consequent coverage of vaccination at 3 months of age will be considerably lower than when given in the neonatal period when the babies are in effect a 'captive' population. In the study reported, at the end of the first year 7% of those immunised in the neonatal period did not have a BCG scar as against 0·6% of those immunised at 3 months.[1] I would suggest that even in this country, if BCG was planned to be given at 3 months the number of children not immunised would far exceed 7%, and that as a result although the immunisation itself was more effective, the protection from tuberculosis itself will be less powerful. The risk of serious complications after immunisation (lymphadenopathy with fistulisation) was not significantly different between the groups.

It would, therefore, seem hasty to change any immunisation programme until further evaluation had taken place.

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1 Ildirim I, Sapan N, Cavusoglu B. Comparison of BCG vaccination at birth and at third month of life. *Arch Dis Child* 1992;67:80–2.

Dr Ildirim and colleagues comment:

We read with interest the letter of Dr Gorham and are pleased to learn that Dr Gorham accepts that immunisation is more effective at the end of the third month.

We do not agree that the number of children coming for vaccination will be fewer at the third month. As more than half of deliveries are not performed at maternity hospitals in developing countries, to reach the newborn for BCG vaccination will be more difficult in those countries. Instead every developing country has a vaccination programme (diphtheria, pertussis, tetanus, and polio) for children, starting in the second

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BOOK REVIEWS

Modern Perspectives of Child Neurology. Edited by Y Fukuyama, S Kamoshita, C Ohtsuka, and Y Suzuki. (Pp 360; price not stated, hardback.) The Japanese Society of Child Neurology, 1991.

This book consists of a series of papers presented at the Joint Convention of the 5th International Child Neurology Congress and the 3rd Asian and Oceanian Child Neurology Congress in Tokyo in 1990. There are contributions from some leading figures in the field of child neurology. The topics covered provide a comprehensive account of various neurological conditions, some pertaining to children of a particular background including the tropical countries. The remaining conditions notably febrile convulsions, epilepsy, metabolic disorders, and neuromuscular disorders have a wider emphasis and are less likely to be influenced by the country of origin. The diagnostic power of magnetic resonance imaging and computed tomography scanning is widely accepted but equally important are contributions from biochemistry, genetics, and virology in clinical diagnostics. There are new ideas put forward in management from advances in psychology, pharmacology, and molecular biology. The development of rehabilitation services for children are discussed in socioeconomic circumstances that vary from a country with an advanced economy to others that are less well off. An attempt to set up such a service is highlighted in a slum area where children with mental handicaps had been identified.

There are nine parts to this book and within each part are subsections consisting of papers presented at this meeting. The topics selected include metabolic encephalopathies; neurological infections in childhood; immunisation and child neurology; febrile conditions and their outcome; intractable epilepsies in infants and children; learning disorders in children; newer treatment for neuromuscular disorders; rehabilitation and child neurology; and neurology in tropical countries. A variety of information is incorporated within each part through a selection of papers with authors from different countries. Part 1 for instance, opens with three subsections including acquired encephalopathies with a Reye or Reye-like presentation; chronic encephalopathy with ragged-red fibres: with particular references to mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS); and Leigh's syndrome: clinical and biochemical correlates. Some of the remaining parts of the book tend to be more extensive with five to seven subsections each related to a common theme.

The information presented is both understandable and useful to the clinician. There are extensive lists of references which would be valuable to those involved in research. The printing, illustrations, and the tables are of high standard on good quality paper. The contents are well set out, though it would have been helpful to have had an index section at the end of the book. *Modern Perspectives of Child Neurology* is not a conventional textbook dealing with diseases of the nervous system in children but it is a timely text containing information on many advances in child neurology of the 1980s. Though largely directed towards the specialist a significant advantage of this book is that it contains information for the general paediatrician with an interest in neurology.

S W D'SOUZA
Senior lecturer and consultant paediatrician

The Pediatric Anesthesia Handbook. Edited by Charlotte Bell, Cindy Hughes, and Tae Hee Oh. (Pp 626; £26 paperback.) Mosby-Year Book, 1991. ISBN 0–8016–0230–0.

Each chapter of this book starts with a short poem or nursery rhyme relevant to the chapter contents. The quotation at the beginning of the chapter on newborn resuscitation reads 'Where did you come from, baby dear? Out of everywhere into here'. Suitably modified this quotation could have formed a preface for the book: 'How did we write you baby dear? We put everything into here'.

This handbook covers paediatric anaesthesia, resuscitation of the newborn, preoperative assessment, postoperative recovery and pain relief, and some elements of paediatric intensive care. It is designed as bench book, is spiral bound, and of a size that would fit in a white coat pocket, just. The book mixes standard text and tables to good effect and each chapter has a reaonable bibliography including references as recent as 1990. Much of the information in this book is excellent—in particular the chapter on paediatric syndromes and anaesthetic implications is the most useful I have seen anywhere.

What criteria do we require in a bench book? Firstly it must be easy to use. In some respects the editors achieve this, the standard of the tables is very high and they provide easy access to a great deal of information. The index, however, is very poor and makes it difficult to find the information. Although there is an account of anaesthesia for the infant with pyloric stenosis, neither pyloric stenosis, nor Ramstedt's procedure appear in the index. Secondly the information provided has to be accurate and complete. There are too many inaccuracies and omissions for this to be the case. The section on acute epiglottitis does not include any details of antibiotic treatment. In addition for British anaesthetists many of the techniques described, while acceptable in North America, are less relevant this side of the Atlantic.

The preface indicates that the book is intended to be for junior anaesthetists and non-paediatric anaesthetists who anaesthetise children, if this is the case it would seem difficult to justify the amount of material only of relevance to specialist paediatric anaesthetists, for example paediatric liver, cardiac, and heart-lung transplantation and neonatal anaesthesia. There is certainly a need for a bench book in paediatric anaesthesia, unfortunately this book does not succeed and I cannot recommend it to British anaesthetists.

S G GREENHOUGH
Consultant paediatric anaesthetist

Fragile X Syndrome—Diagnosis, Treatment, and Research. Edited by Randi Jenssen Hagerman and Amy Cronister Silverman. (Pp 378; £61 hardback.) Johns Hopkins University Press, 1991. ISBN 0–8018–4169–0.

The fragile X syndrome is characterised by X linked mental retardation and very little else—no dramatic physical features to aid diagnosis, no reliable diagnostic test to detect carriers, and no explanation of the bizarre observation that an unaffected male can be a carrier for the condition.

This all changed in 1991: the enigma became a multimedia star. A unique mutation mechanism was discovered, the molecular basis of the mode of inheritance was published, and new, precise diagnostic methods became available. A stretch of DNA within a gene on the X chromosome can become unstable, increase in length in succeeding generations, and disrupt the function of the gene. So much for the exciting molecular genetics—what about the patient?

The editors of this book on fragile X syndrome seek to provide a contemporary review of this disorder. The scope of the book is appropriately wide, and the audience is meant to include clinicians and paramedical professionals. Part I is diagnostic in flavour, with chapters on the physical features in males and females, epidemiology, cytogenetics, DNA studies, neuropsychology, differential diagnosis, and theoretical models that account for the unique mode of inheritance. Part II is directed more towards management with chapters on genetic counselling, medical care, pharmacotherapy, psychotherapy, and education. Many of the authors are from Denver, Colorado, and this volume represents their many years of experience at the Children's Hospital there.

The strengths of this book are in the clinical and management chapters. In particular, the chapters on the physical presentation, neuropsychology, and education are excellent; these chapters alone are sufficient to justify a position for this book on the shelves of general paediatricians or therapists dealing with children. The otherwise excellent chapter on differential diagnosis is marred by poor photographs. The elements of family counselling and medical care are well summarised.

Unfortunately for the authors and editors, the rapid progress made in fragile X research last year has rendered much of the information about molecular genetics, carrier detection, and family studies out of date. The editors have added brief notes at the end of appropriate chapters, but anyone involved in counselling families with this disorder must follow the current literature. Notwithstanding this problem of timeliness, the chapter on DNA studies is very inadequate. Conventional genetic linkage studies still have a role in counselling families with this disorder. Such studies are expensive and time consuming, yet no attempt is made to discuss efficient and effective strategies for linkage analyses. The information required for accurate genetic counselling of families is spread over the chapters on epidemiology, DNA studies, and counselling, and hence is difficult to draw together.

This book is a useful clinical review of a common and devastating disorder, but it is not comprehensive. The fragile X syndrome accounts for a third to a half of all X linked mental retardation. An introductory overview to place the fragile X syndrome in this context and to summarise the main features and dilemmas would have been helpful. One key issue that is not addressed is the role of genetic registers—the ethical use of such a register, the cost and logistics, and appropriate long term management of families.

GRAEME SUTHERS
Nuffield fellow and honorary associate in medical genetics

Pediatric Cardiovascular Imaging. Edited by Ina Tonkin. (Pp 288; £57 hardback.) W B Saunders Company, 1992. ISBN 0-7216-3665-9.

The practice of paediatric cardiology has been revolutionised by the widespread use of high resolution cross sectional and Doppler echocardiography to provide the accurate morphological and haemodynamic diagnoses necessary for optimal management of children with congenital heart disease. Since the mid-1980s, the use of diagnostic angiography has, therefore, been increasingly restricted to complex lesions, such as pulmonary atresia with multifocal pulmonary blood supply, and to older patients with poor echo windows. Recently new methods of imaging and access have been introduced: magnetic resonance imaging (MRI), ultrafast computed tomography, and transoesophageal echocardiography. All are vying with each other and conventional investigations to find a place in the assessment of these patients, despite the relatively high costs in hardware and training. A textbook that provided a logical and rational approach to this array of diagnostic imaging techniques in the context of the whole spectrum of congenital heart pathology, while taking into account the differing needs of the fetus, neonate, child and adolescent, would be of great value. At first sight this book should provide just such an insight for the training and paediatric cardiologist or radiologist.

Unfortunately the authors, who mainly come from the American mid-west, have not achieved this. The main fault is the sparse recognition of the eminence of echocardiography in day to day clinical practice. There is a striking contrast between the 34 page chapter on echocardiography and the dominant 94 page chapter on angiography. No mention is made in the echo section of lesions such as Ebstein's anomaly (except under fetal echocardiography), common arterial trunk, hearts with univentricular atrioventricular connection (including tricuspid atresia), or cor triatriatum; yet they merit relatively long sections in the angiography section. One would be forgiven for the impression that echocardiography is merely an adjunct to angiography for most patients, including sick neonates. Perhaps this reflects the radiological background of most of the authors, as the opposite is currently the case in most paediatric cardiology centres. There is no mention of transoesophageal or intraoperative echocardiography, both of which are of increasing importance.

There is much duplication of the anatomical and therapeutic descriptions of the various lesions throughout the book and perhaps these would better have been summarised in one of the first two chapters. Readers in training may find some of the terminology confusing as terms such as 'single ventricle' are rarely used in UK centres. No comparison of merit for specific lesions is made between angiography (invasive), MRI, and ultrafast computed tomography (expensive) and echocardiography as they are largely isolated in their individual chapters and it is difficult to know the best place for these various investigations in every day clinical practice.

On the positive side, the chapters on plain film radiography, interventional catheterisation, and fetal echocardiography give good accounts of their usefulness and importance and the illustrations are of high quality. However, the problems listed above make it difficult to recommend this book.

RODNEY FRANKLIN
Consultant paediatric cardiologist

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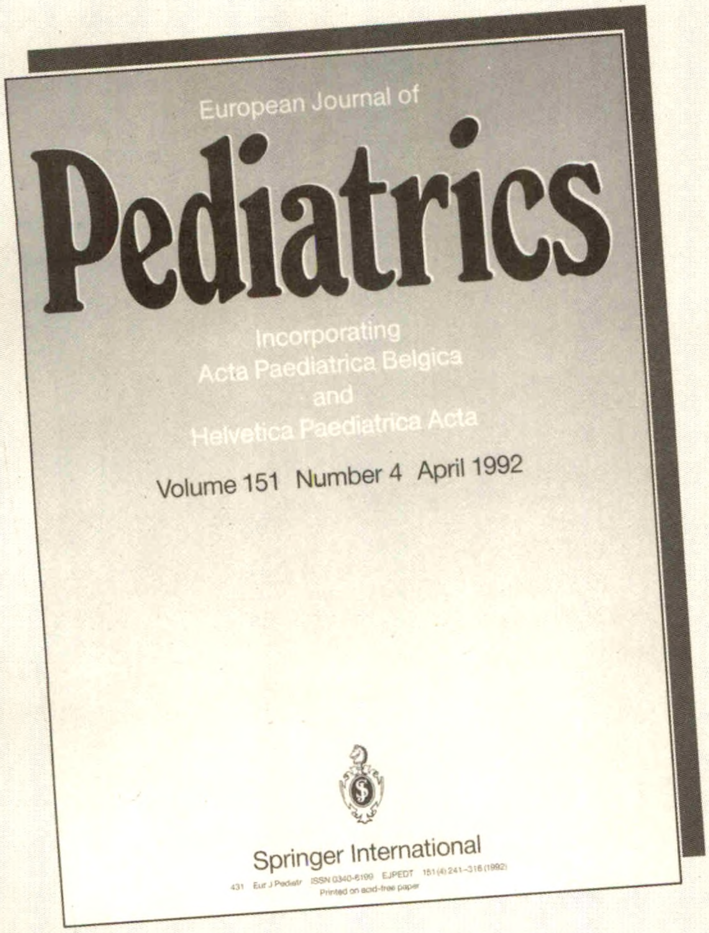

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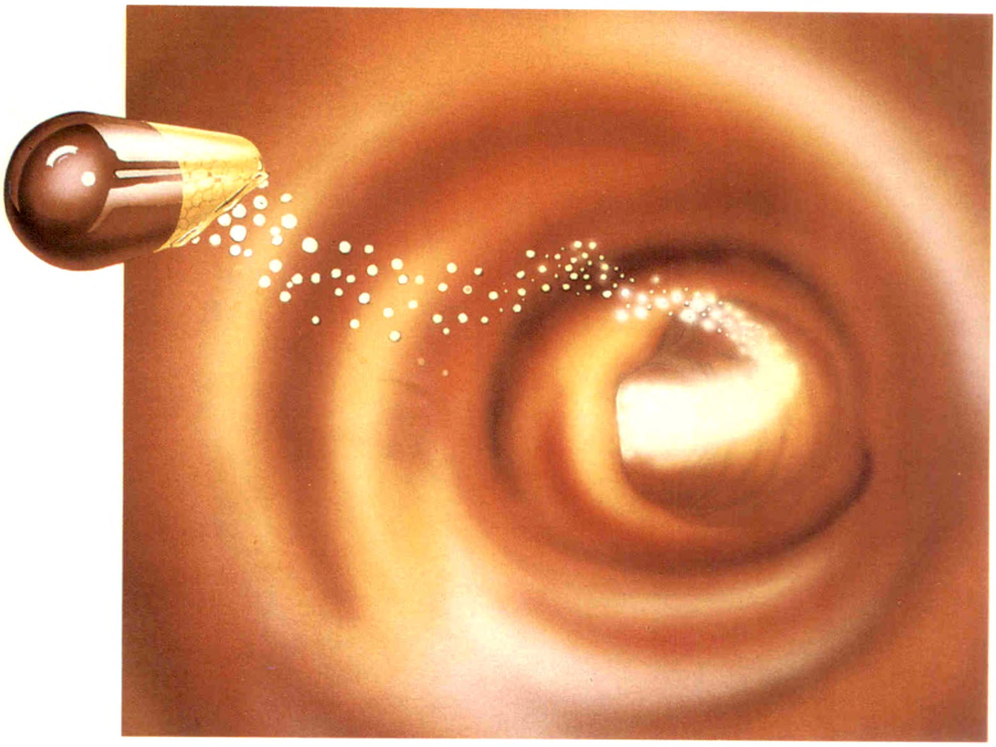

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Annotations

Does cytomegalovirus present an occupational risk?

When cytomegalovirus (CMV) infection is raised as an occupational health issue, this usually relates to an immediate situation. For example, a child with congenital cytomegalovirus infection has been admitted to a nursery; what advice should be given to the pregnant nursery assistant? A nurse looking after an infant with symptomatic congenital cytomegalovirus in a special care baby unit realises she is pregnant; should she be advised to have a blood test to determine her cytomegalovirus status?

In healthy individuals cytomegalovirus infection is usually asymptomatic and, as a result, few people are aware of their cytomegalovirus status. In the UK seropositivity rises from around 20% in early childhood to over 80% in late middle age.[1 2] Once acquired, the virus becomes latent and, like other herpes viruses, may reactivate throughout life. Both the primary infection and any recurrences are likely to result in virus shedding in the urine and other body fluids.

Infection may have serious consequences for individuals who are immunocompromised, however, for instance those undergoing cancer treatment or having transplant surgery, people with HIV infection, and very premature infants. Infants born with congenital cytomegalovirus infection are also at risk, overall about 10% of them will have long term sequelae attributable to cytomegalovirus, the most frequent defect being sensorineural hearing loss; approximately half the affected children have severe physical and/or intellectual handicap.[3] Nevertheless, about 90% of congenitally infected babies will develop normally.

Transmission of infection

Congenital cytomegalovirus infection can result from both primary and recurrent maternal infection at any stage of pregnancy.[4] While congenital infection is comparatively rare, occurring in approximately 3/1000 births in the UK, cytomegalovirus is commonly transmitted from a seropositive mother to her baby at the time of delivery or in the early months of life. About one child in five has acquired infection by 12 months and virus excretion may continue for several years in normal healthy children.[1 5]

In a population where many people escape cytomegalovirus in early childhood, sexual transmission plays an important part in adult acquisition of infection. Like other sexually transmitted diseases, cytomegalovirus seropositivity is associated with the number of sexual partners and inversely with the use of barrier contraception.[6] Blood transfusion and organ transplantation are also effective, but less common, routes of transmission.

Family studies have shown that when a young child or baby acquires the infection, for example from a blood transfusion, most other susceptible household contacts seroconvert over the next few months. However, this is not an airborne infection and casual contact presents little opportunity for transmission of the virus. Close, prolonged, and intimate contact such as that which occurs between children and adults in a family is required.

Health care settings

Many hospital patients excrete cytomegalovirus at some time during their hospital stay. For example, a substantial proportion of children on a paediatric ward are likely to be shedding the virus in their urine, it is common for seropositive women to excrete the virus from the cervix, and cytomegalovirus disease is a well recognised complication in immunosuppressed individuals, such as those with HIV infection. In a Minnesota hospital 12% of patients on the acute care renal ward shed cytomegalovirus during their hospital admission.[7]

Many health professionals with occupational exposure to cytomegalovirus are women of childbearing age. There have been several instances where an individual patient has been thought to be the occupational source of cytomegalovirus infection in a pregnant nurse or doctor. However, restriction enzyme analysis of cytomegalovirus DNA from the suspected source and the congenitally infected infant, or the products of conception, have shown the virus strains to be dissimilar and have excluded the suspected source of infection in all the published case reports to date.[8 9]

Many epidemiological studies have investigated cytomegalovirus seroprevalence and seroconversion rates among health professionals. These studies suggest that rates of acquisition of the virus are similar to those found in the general population, and that hospital staff are not at increased risk of acquiring cytomegalovirus infection, even if they are working in paediatric, neonatal intensive care, or acute renal units.[7 10] It is likely that this reflects the protective nature of normal infection control procedures within the health care setting.

Day care settings

Three recent studies in the US have identified unexpectedly high rates of seroconversion among daycare workers.[11–13] Differences in the organisation of daycare, including the number of children catered for, their age mix and social background, as well as different patterns of acquisition of cytomegalovirus infection in different communities, may explain why these findings have not been reported elsewhere. There is no evidence to suggest that cytomegalovirus infection is a particular problem in British nurseries or playgroups.

Nevertheless, it is reasonable to assume that nursery staff do not routinely practise the kind of infection control procedures carried out in hospitals, but deal with children more as one would at home. Many of these workers come into daily contact with large numbers of young children, some of whom will be excreting cytomegalovirus in saliva or urine.

The growing awareness that nursery staff may be exposed to many infections, including hepatitis B and HIV, has highlighted the need to ensure that high standards of hygiene are maintained within the day nursery. In this context, the overall standard of hygiene practised within a day nursery should be more than adequate to prevent the acquisition of cytomegalovirus. Health education about infections in the community, including cytomegalovirus, should include information about their modes of transmission and means of control, and be a fundamental element in the training of nursery staff and other professionals working with young children in the community. As far as cytomegalovirus is concerned, particular attention should be paid to avoiding the exchange of saliva, and hands should be washed after changing nappies or helping children to use the toilet.

Individual concerns

To return to our opening example: the congenitally infected child in a day nursery is just one child likely to be excreting virus intermittently alongside many others who will not be recognised. The pregnant nursery assistant can continue to care for that child along with all the others, and this can include changing nappies or helping the child use the toilet, as long as the caregiver washes her hands thoroughly afterwards. She can also cuddle and comfort the child, although practices which might involve the exchange of body fluids, such as exchanging wet kisses or half eaten food should be avoided, not just with a child known to be excreting cytomegalovirus, but with any child.

The pregnant paediatric nurse looking after the infant with congenital cytomegalovirus should not automatically be advised to have blood tests to ascertain her cytomegalovirus status. Under normal circumstances she is extremely unlikely to have acquired an infection from this source. If a recent or current infection were to be diagnosed, invasive investigations could determine whether the fetus was infected (about two in three escape infection) but not whether it was the one in 10 who would be damaged.[14] Cytomegalovirus infection in pregnancy can cause damage at any stage of gestation and for most women who seroconvert in pregnancy the information is likely to come too late for termination to be a realistic option. There is no treatment to offer.

Recommendations

- Children known to be excreting cytomegalovirus should not be excluded from nurseries or any other situation. They constitute only a small proportion of infectious children, most of whom are asymptomatic and unrecognised. There is no reason to screen patients or children routinely for cytomegalovirus excretion. A significant proportion will be shedding virus, and the absence of virus on one occasion does not exclude infection as shedding is intermittent. The assumption must be that anyone might be infectious.
- Occupational exposure to cytomegalovirus infection is only one of many reasons for encouraging adherence to infection control procedures in hospital settings.
- In nurseries and other community settings providing for the care of young chidren, proper facilities for reasonable hygiene should be ensured, and their use encouraged. It is reasonable to suggest that pregnant women who work with young children should minimise the kind of contact that might involve the transfer of saliva, and should wash their hands thoroughly after changing nappies or carrying out other intimate tasks. There must be adequate handwashing facilities for staff, washbasins should be located near to where nappies are changed, and there should be proper arrangements for the disposal of used nappies.
- Neither nursery nor hospital staff should be routinely screened for cytomegalovirus status. This is a common infection, there is no clear advice to be given on the basis of results from a screening exercise, and there is no vaccine available. Staff should receive good health education about cytomegalovirus and other infections they are likely to encounter, and understand the reasons for practising good personal hygiene.
- Everyone is exposed to asymptomatic cytomegalovirus excretors not only at work but also in their social and family life, where intimate contact and transmission of infection is far more likely than at work. Nevertheless, individual pregnant staff may have particular anxieties which should be managed sensitively.

Detailed guidelines have been drawn up by various groups working in North America,[15–18] similiar to those outlined here. However, further research is required to establish whether or not transmission of cytomegalovirus infection to day nursery staff does occur in the UK.

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Aetiology of malocclusion of the teeth

Malocclusion of the teeth is not itself a disease, although it can be caused by pathological processes or injury, and can predispose to pathological changes such as caries and periodontal disease. It is not peculiar to the human race, having been observed in a wide variety of mammalian species. Some malocclusions involve no more than misplacement of individual teeth, but others, particularly among the primates, affect groups of teeth or even the whole dental arch.[1] Minor degrees of malocclusion have been found in primitive man, and there is evidence that modern man, living under primitive conditions, is not entirely free of malocclusion or irregularity of the teeth, albeit less frequently and less severely than those living in civilised communities.[2–4]

Hybridisation has been shown by Stockard to produce quite severe malocclusion in dogs.[5] It has been suggested by Hunt that one of the effects of civilisation as we know it has been to provide greatly increased opportunities for hybridisation, or intermarriage, and he speculates how much this contributes to malocclusion in modern man.[6]

Normal occlusion of the teeth

Any discussion on the causes of malocclusion should be held against a background understanding of normal occlusion as malocclusion is, by definition, a departure from normal occlusion. As each tooth erupts it is guided by the interdigitation with the opposing teeth into a correct relationship based on the morphology of the teeth. Thus the upper incisors should overlap the lower incisors by about one third of their length, and each upper premolar and molar should occlude a little outside and behind its lower homologue. Thus a tooth by tooth description defines the relationship of each tooth within and between the two arches.[7] In the course of this, the mandible is growing forward relative to the maxilla, a process which should continue well into adulthood. It should be reflected in the way the teeth fit together, but this is likely to be inhibited by interlocking of the tooth cusps when they are not worn down during development.

Local causes of malocclusion

Abnormalities of tooth number, form, or position may cause local irregularities and consequent malocclusion. Extra teeth are found in about 1% of children, and may either resemble teeth of the normal series or have conical or invaginated crowns. Apart from wisdom teeth, congenital absence of teeth occurs in about 4% of children. The condition is often familial. Occasionally missing and extra teeth have been found in the same mouth, suggesting that the two might have a common origin, namely a defect of tooth budding. Extra teeth are usually found in the incisor region, but the upper lateral incisor and lower second premolar are the teeth most frequently missing. Absence of an upper lateral incisor on one side may be accompanied by a diminutive lateral on the other. One might speculate whether they are two stages in an evolutionary reduction of the number of our teeth. A further complication of these cases might be the ectopic eruption of the upper canine when it is deprived of the guidance it normally has from a full size lateral incisor.

Loss of a tooth by extraction or by traumatic injury allows migration of adjacent teeth into the vacated space. If the tooth is a deciduous molar, the successional tooth may become excluded from the arch of teeth. Traumatic injury of a deciduous incisor frequently causes death of its pulp. Subsequent failure of the root to be absorbed will guide the successional incisor to an abnormal lingual position. Anchylosis of a tooth, usually a deciduous molar, prevents it from moving occlusally with the other teeth, and often delays its being shed. As a result the successional tooth erups ectopically. Biederman found this condition to affect homologous teeth of each side much more frequently than opposing teeth.[8] He concluded that the cause is more likely to be disturbance of the process of root absorption and compensating apposition of alveolar bone than to be caused by excessive force on the occlusal surface.[8]

Growth of the facial bones

Any disturbance of jaw growth is likely to be reflected in the occlusion of the two sets of teeth. Factors which determine the way bones grow are therefore relevant to the aetiology of malocclusion. In studying the resemblance of the skull in identical twins, it was observed that the similarity was much stronger for individual bones than for the skull as a whole.[9] It is suggested that there is some lattitude in the way bones fit together in the skull. This is of some importance as the upper and lower teeth are mounted in different bones.

It has been shown in a series of animal experiments that the head can be considered as being made up of mutually dependent functional cranial components.[10] Each component comprises a skeletal unit which has a biomechanical role, and a functional matrix whose activity determines the form of any skeletal elements within it. Thus vigorous use of temporalis muscle will enhance the strength and size of the coronoid process. Indirectly it will also influence the alveolar process by virtue of reactive forces from the teeth when they are brought into occlusion. Because the teeth are part of the skeletal unit they also become subject to some modification. This is achieved by attrition and wear of the occlusal and interproximal surfaces of each tooth.

Abnormalities of dental arch relationship

Although heredity is undoubtedly of importance in determining the relationship between upper and lower dentitions, there is no single gene responsible. Hereditary influences are more likely to be polygenic and may also have indirect influences. One example of this is achondroplasia, in which impaired growth in the cranial base inhibits forward translation of the maxillary complex, causing it to appear retrognathic.[11] Studies on twins have suggested that genetic control may be stronger for facial height than for facial depth.[12 13] Thus cases with extremes of incisor overbite associated with extremes of lower face height appear to have a strong familial tendency. Mandibular prognathism due to excessive mandibular growth is also an inherited character.[14]

Mouth breathing has been shown to cause the mandible to grow in a more downward direction at the expense of some forward growth. At the same time upper and lower incisors become inclined more lingually with a tendency to an open bite and a crossbite.[15] Correction of the mouth breathing as a result of treatment has been shown to allow spontaneous reversal of these effects.

Many congenital malformations involve malocclusion of the teeth. Of these the most frequently seen are clefts of the lip and palate. Evidence of ethnic, familial, and twin studies suggest that heredity plays an important part in the aetiology of clefts of the lip and primary palate, but not in that of an isolated palatal cleft. Research has shown that unilateral clefts in both animals and man occur twice as frequently on the left side as on the right. At the time the primary palate is being formed, the artery supplying the right side provides the shortest and most direct blood supply from the heart.[16] This suggests that impairment of the blood supply may be a factor in localising the side of the cleft.

Hemifacial microsomia includes some rare congenital craniofacial malformations which occur unilaterally. They are believed to arise from an expanding focal haematoma which forms in the region of the stapedial artery at a critical stage of morphogenesis. This causes non-selective destruction of differentiating tissue in the vicinity of the ear and jaw.[16] On the other hand, mandibulofacial dysostosis includes deformities which occur bilaterally and are thought to be inherited as an autosomal dominant trait. They affect the malar bones, ears, and mandible symmetrically, but there is wide variation in their expressivity, even in the same family. Such massive disturbances of growth have a profound effect on the occlusion of the teeth.

Crowding of the teeth

The most prevalent cause of malocclusion in modern man is crowding of the teeth, which appears to arise from a disproportion of size between the teeth themselves and their supporting bone. Moderate and severe crowding affects about one fifth of British subjects.[17] Comparison of crowded and uncrowded cases has shown that the arch size is smaller in crowded cases, and to a less extent the teeth are larger.[18] Growth of the jaws, in common with that of the body generally may, under adverse nutritional conditions, fail to achieve its full genetic potential.[19] The crown size of teeth is largely determined genetically[20], and is established well before growth of bones is complete. Like other epithelial tissues, such as skin and finger nails, tooth enamel should be subject to progressive loss of substance in the course of function. The amount depends on the physical properties of the diet, and the vigour with which the jaws are used for this and other purposes. There is consistent evidence of appreciable attrition on both the occlusal and interproximal surfaces of the teeth in all specimens of primitive man, and in surviving populations living under stone age conditions.[21] Study of the development of their dentitions has shown that the interproximal wear occurs as the teeth erupt, and as much as 14 mm of tooth substance can be lost from the sum of tooth widths.[2–4]

The interdental space created by the loss of tooth substance closes up as the wear occurs. Experimental evidence suggests that approximal contact between the teeth is normally maintained by continual contraction of the transeptal fibres of the periodontal membrane.[22] This is essential to protect the interdental papillae from damage. The wear causes flattening of the interproximal surfaces in such a way that it enhances the stability of the dental arch.[2–4] Studies of people living under stone age conditions have shown that the reduction of tooth height by occlusal wear is compensated by continual eruption of upper and lower teeth up to the age of 40, thus maintaining the lower face height.[23] The two processes are complementary but are independent of each other. In other studies it has been found that the continued eruption of teeth occurs also in modern man living under civilised conditions, even though attrition has not occurred.[24] There is therefore slow but measurable increase in lower face height, and this is accompanied by some downward and backward rotation of the mandible. The absence of attrition means that the teeth retain their original size, but the jaws are no bigger than those of our ancestors. This is undoubtedly one factor in the aetiology of crowding. Preservation of point contact denies to the modern dentition the stability which should be afforded by flattened interproximal surfaces. As a result a mild irregularity may become worsened as the transeptal fibres of the periodontal membrane contract.

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ORIGINAL ARTICLES

Heart-lung transplantation: all the facts

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Abstract

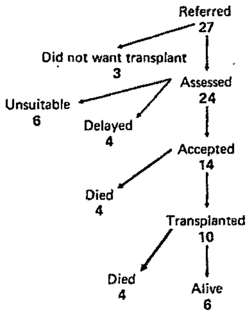
Of 27 children referred for assessment of suitability for heart-lung transplant, 10 (37%) were actually transplanted. Six are still alive from three months to three years since operation. Two thirds of the cohort have died at various stages during referral, assessment, and transplant. While the transplant has offered miraculous new life to a few children, many more have experienced increased and unnecessary suffering. Planning of transplant programmes must take all facts into account. The possibility of heart-lung transplant must not deter further efforts to control chronic lung diseases medically and must not influence appropriate terminal care.

Heart-lung transplantation is now presented as a practical treatment for children in terminal respiratory failure. Preliminary results would suggest that survival rates after transplantation are at least as good in children as in adults. A recent publication presented details of five children, alive and well, 5–17 months after heart-lung transplantation all of whom had returned to activities normal for their age. Two had primary pulmonary hypertension, two cystic fibrosis, and one Eisenmenger's syndrome. The paper presented the details of the progress of these five patients.[1] It did not elaborate on the fact that they came from 33 children who were initially referred to the transplant programme. Little comment was made on the problems that must inevitably have arisen among the 28 children who were either considered unsuitable for the programme, died waiting, or were still awaiting transplant.[2] However, this must be balanced against the inevitable demise that would have occurred in all the patients who received heart-lung transplantation, had this not been possible.

The Paediatric Respiratory Unit at the Royal Brompton and National Heart Hospital has been referred children for assessment of suitability for heart-lung transplantation and this paper details the outcome in all the patients referred over a three year period.

Patients (figure and table)

Over a three year period, from March 1987 to March 1990, 27 children were referred to the unit for assessment. There were 15 girls and 12 boys aged between 5 and 16 years at referral. Twenty two had cystic fibrosis, two cryptogenic fibrosing alveolitis, one idiopathic pulmonary hypertension, one a combination of very severe emphysema with pulmonary haemosiderosis, and one pulmonary fibrosis caused by cytotoxic treatment and irradiation.



Heart-lung transplant in children.

SELECTION CRITERIA

Children were considered candidates for heart-lung transplantation if their lung function was less than 30% of predicted standards for height and was continuing to deteriorate. For chronic obstructive disease, as in cystic fibrosis, forced expiratory volume in one second was taken as the key index; for restrictive disease, as in cryptogenic fibrosing alveolitis, vital capacity was used. The children were also required to have a severely impaired quality of life, and an oxygen saturation of $<90\%$ even on minimal exertion. Finally when in possession of all the facts about heart-lung transplantation, they still had to have a desperate desire to procede. Absolute exclusion criteria were poor compliance with treatment, which was usually associated with adverse psychosocial circumstances, current high dose corticosteroid treatment, impaired renal function, and previous pleurectomy. Children with portal hypertension were excluded unless liver transplant was also contemplated. Diabetes mellitus or colonisation with *Pseudomonas cepacia* were not considered absolute contraindications and those with poor nutrition entered a rehabilitation programme including the use of gastrostomy nocturnal drip feeding to make them suitable for heart-lung transplantation.

Results

Of the 27 children referred, remarkably there were three, all with cystic fibrosis, where neither parents nor child had any idea that they were being considered for transplant. Of the 24 children assessed six, all of whom have since died, were considered unsuitable for heart-lung transplantation and were not referred on to the surgeons, and four had their inclusion on the

Outcome of assessment for heart-lung transplantation

Decision	*No of children*	*Disease*	*Detail*	*Dead/ alive*
Did not want transplant	3	Cystic fibrosis	Preterminal: died at home within one month of referral	Dead
		Cystic fibrosis		Dead
		Cystic fibrosis	Increased medical treatment: alive one year later	Alive
Unsuitable	6	Pulmonary fibrosis after bone marrow transplant	Bilateral pneumothoraces, underweight	Dead
		Cystic fibrosis	Tuberculosis of spine	Dead
		Cystic fibrosis	Portal hypertension	Dead
		Cystic fibrosis	Too ill: died within one week of referral	Dead
		Cystic fibrosis	Psychosocial and compliance problems	Dead
		Cystic fibrosis		Dead
Delayed	4	Cystic fibrosis	Lung function >50% predicted	Alive
		Cystic fibrosis		Alive
		Cryptogenic fibrosing alveolitis	High dose steroids being reduced	Dead
		Cystic fibrosis	Responded unexpectedly to methotrexate	Alive
Died on waiting list	4	Cystic fibrosis	Delayed palliation	Dead
		Cystic fibrosis		Dead
		Cystic fibrosis	Hid medication to avoid transplant	Dead
		Cryptogenic fibrosing alveolitis	After steroid withdrawal	Dead
Died after transplant	4	Cystic fibrosis	Acute rejection and infection within one week	Dead
		Idiopathic pulmonary hypertension		Dead
		Cystic fibrosis	Poor heart function: died in three days	Dead
		Cystic fibrosis	Obliterative bronchiolitis 20 months after transplant	Dead
Alive after transplant	5	Cystic fibrosis	3 months–18 months	Alive
	1	Emphysema and pulmonary haemosiderosis	3 years	Alive

programme delayed. One delayed patient, a boy of 14 with cystic fibrosis, had developed a very rapid onset of small airway obstruction in the previous 12 months. This could not be attributed to either chronic pseudomonas infection or indeed any other obvious immunopathology. The disease was partially responsive to very high dose oral corticosteroids. He was started on oral methotrexate as a means of facilitating steroid withdrawal before being put on the waiting list for heart-lung transplantation. However, his improvement on the methotrexate was so dramatic that two years later he has returned to full normal activities with lung function well over 50% of predicted and is now too healthy to be considered for transplant.

Thus 14 patients were considered suitable to be referred on for heart-lung transplantation and were placed on the waiting list. Four children have died on the waiting list two of whom, both with cystic fibrosis, had a significant delay in institution of palliative treatments, and as a result suffered a great deal more discomfort and distress than would be considered acceptable in the terminal phase of any illness. The third girl with cystic fibrosis who died on the waiting list indicated to her parents, shortly before death, that she did not wish to have a transplant and had, in fact, failed to take any of her medical treatment for the previous two weeks. She had stored this in a polythene bag and hidden it in her locker. She presented the bag full of medications to her mother. Subsequently it transpired that she had talked to another of the patients on the ward, indicating very vehemently that the only reason she had agreed to be put on the waiting list was for her parents' sake. They were, at the time, in the process of separating and divorcing. The fourth patient who died waiting had cryptogenic fibrosing alveolitis, and deteriorated rapidly after withdrawal of steroids as a prelude to transplantation.

Ten patients have received transplants: eight with cystic fibrosis and one each with emphysema combined with pulmonary haemosiderosis and idiopathic pulmonary hypertension. Four children have died after heart-lung transplantation; one boy with cystic fibrosis lasted only three days. His new heart never functioned properly and he died during an attempted second transplant. One girl with cystic fibrosis died 10 days after transplant with acute rejection and septicaemia; the second girl with cystic fibrosis died 20 months after heart-lung transplantation with obliterative bronchiolitis. A 13 year old girl with idiopathic pulmonary hypertension, stable over the previous eight years, was entering puberty and considered to be at high risk of death at sometime in the next few years. Though having severe cyanosis and considerable exercise limitation, she and her mother considered her life to be happy and fulfilled. She died within one week of transplant probably of acute rejection. This leaves six children who are alive in relatively good health, between two months and three and a half years after heart-lung transplantation. However, none has been spared the inevitable acute rejection episodes nor periods of sepsis.

Discussion

Heart-lung transplantation is now being presented as the ultimate treatment for terminal respiratory failure and its existence has given new hope to a large number of patients and their families facing the prospect of premature death.[3] The success of this procedure in adults has inevitably led to its extension to the paediatric age range and the preliminary results are at least as good as in adults.[1] The experience of seeing a child in terminal respiratory failure miraculously given new life after a heart-lung transplantation can only encourage an intensely optimistic and positive approach to the procedure, but a balanced perspective of the pros and cons has been sadly lacking from publications.

The Papworth experience published in 1989 indicated that only five of 33 (15%) who were referred for heart-lung transplantation actually benefited from the procedure over an 18 month period.[1] Five were considered unsuitable, eight were on a provisional waiting list of whom four had died, and four were still waiting. Of the 15 accepted on to the transplant programme two had died waiting and eight were still waiting.[1] The figures I have presented over a three year period show 10 of 27 (37%) have ultimately received a transplant. I have deliberately excluded consideration of any patients who have been assessed over the last six months in order to give a complete presentation of the ultimate outcome. Thus the figures are comparable.

The three patients who were referred without adequate discussion about heart-lung transplantation between patient, parents, and referring physician were clearly handled extremely badly. The unnecessary transporting to an alien hospital under such circumstances was unforgivable and totally avoidable. Hopefully this problem will not recur. This leaves 10 of 24 (42%) who have been transplanted after assessment.

It is to be hoped that more appropriate referrals will be made in the future to reduce the numbers who are clearly unsuitable for heart-lung transplantation. The recrimination that is inevitable between the patients, parents, referring doctor, and the assessing doctor is very unpleasant for all concerned and causes immense upset for staff, parents, and patients alike. Firm handling at an early stage, indicating that certain medical circumstances preclude transplant, would prevent much of this difficulty arising. However, ultimately a third party may be required to provide an authoritative opinion. It has been particularly difficult to handle the patients who, for various reasons, have very poor compliance with treatment. This must be an absolute contraindication to transplant because rigid adherence to the immunosuppressive regimen after transplant is imperative. Missed doses of cyclosporin would be a death sentence. Equally adverse psychosocial circumstances, which are difficult to assess, will remain a contraindication but independent assessment by a psychiatrist will be required.

Some patients may be placed on a 'holding list' either because they are still reasonably healthy or because other adjustments to medical treatment are required before the patients are suitable for transplant. It is to be hoped that most of these patients will be found more effective medical treatment that will avoid the necessity for heart-lung transplantation. Only patients who have received maximal treatment and have failed with such approaches should ultimately end up on a transplant programme.

A total of 71% of those children accepted on to the programme have ultimately received a transplant. One suspects that in the future this figure will be very much lower as many more children who might be deemed suitable for heart-lung transplantation will actually be transferred to the transplant centres. Six of 10 are still alive after transplant. All have had acute rejection episodes and infections that have necessitated intensive medical supervision.

Even these figures do not give a clear representation of the anguish and suffering that is borne by the children and their families. Geographical and social dislocation during assessment and the subsequent wait for transplant and indeed the period of intensive medical care after transplant causes enormous problems. Indeed one of the successfully transplanted boys was faced with his parents' divorce after the procedure. His mother stayed in hospital with him for the nearly six months of inpatient treatment. Unfortunately, the family home was too far away for regular paternal visits. His parents' relationship broke down during the prolonged enforced separation.

A more exquisite form of torture could not be devised than to give a child with rapidly failing health a bleep that will sound once a week as a check and will go off once at any time in the future to indicate that suitable organs may have been found. As death approaches the desire to avoid palliative treatment can lead to totally unnecessary suffering. The issue of whether to use artificial ventilation when irreversible respiratory failure supervenes raises enormous medical and ethical problems. Intensive care units could very easily become blocked by children in respiratory failure being ventilated while awaiting transplantation. The results of heart-lung transplantation on patients who are being ventilated appears to be poor and therefore perhaps this is not a major issue.[4] It is most important that children in terminal respiratory failure are given appropriate treatment so that they die peacefully, with dignity, and certainly without pain. The patient and parents' grim determination to struggle on to the bitter and painful end is understandable but must be resisted.

The boy who died within three days of transplant had initially been assessed over 18 months before the procedure. At that stage he was very underweight and a poor complier with treatment. However, the use of gastrostomy tube feeding at night and an intensive programme of psychosocial support resulted in him gaining a considerable amount of weight with an improvement in his therapeutic compliance. Eigthteen months of effort in making him suitable for heart-lung transplant culminated in disaster and his parents were clearly left wondering whether the 18 months had produced any tangible benefits. The girl who died 20 months after transplant had a one year period when she was remarkably well and able to sample a relatively normal life for the first time. Before transplant she had been totally resigned to her fate and able to face death in a remarkably mature and appropriate way. In the last six months of her life she became a frightened, desperate girl; she was assailed with morbid guilt about the donor of her heart and lungs and also excessively preoccupied with the child who had received her heart in a so called 'domino' transplant.

The spectre of heart-lung transplantation has fundamentally altered attitudes and medical practice in respiratory clinics. Sadly some families have seriously suggested that hastening deterioration by missing out treatment would lead to earlier transplant and therefore avoid suffering. We have good evidence that steroids are very important in a number of chronic lung diseases including cystic fibrosis but are now more hesitant about their use because of transplantation.[5] Furthermore, pleurectomy is well established as the best treatment for recurrent pneumothoraces in cystic fibrosis but would contraindicate transplant.[6]

At a time of medical rationing with very limited resources in the health service, many paediatricians may question the wisdom of heart-lung transplantation. At present only a third of referrals will benefit from transplant, of whom two thirds may be expected to be alive at least for one year after the procedure. Many will be refused transplant for good medical reasons, and others will die waiting. I believe that heart-lung transplantation must be one final option for some patients in terminal respiratory failure. However, clear guidelines on suitability should be available to all so that unnecessary referral is avoided. Only the most psychologically robust families who fulfil appropriate criteria for severity of respiratory failure and without any of the known medical contrindications to transplant should be referred. Patients and parents should be fully aware of all the facts and figures related to the procedure. Emphasis should, however, remain on prevention, early diagnosis, and effective medical treatment for the management of the vast majority of problems that might ultimately lead to respiratory failure and the need for transplantation. No family should be left in any doubt that heart-lung transplantation is the last resort and will always remain so.

I would like to thank Ms Linda Romain for typing this paper and Ms Joanna Marchant for the diagram.

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Commentary

Heart-lung transplantation is still a new therapeutic option for end stage lung disease. As with any new treatment it was only right that experience in adult patients should be established before extending it to a paediatric population.[1 2] An initial report demonstrated that the procedure was practical and at least in the short term gave similar results to those found in adults.[3]

Three papers in this current issue address three important areas of heart-lung transplantation: namely identification of suitable patients,[4] medium term outcome,[5] and the stresses involved for staff, patients, and their families.[6] The latter presents some of the problems encountered in the first three years of a heart-lung transplantation programme in a single centre. Issues are raised which underline the importance of careful assessment before acceptance onto a transplantation programme and the important point is also made that organ supply is never likely to match demand. However, some improvements in donor supply may come from increased public awareness and the active support of paediatricians and anaesthetists responsible for intensive care. Supply is also limited by the relatively short time (four hours) that organs remain viable once removed from the donor, although there is some hope that this may be extended in the future with improved preservation techniques.[7]

In addition to highlighting important concerns about heart-lung transplantation, the experience presented does seem to have been a rather negative one with many children and their families experiencing 'increased and unnecessary suffering'. Many of the problems identified could in retrospect have been avoided. They indicate a need for greater awareness of potential problems and a high level of honesty, both within transplant teams and within those clinical teams referring patients. Hopefully this is exactly what this and the other two contributions in this issue will go some way towards achieving. Despite the problems of extrapolating from the experience of a single centre to 'all the facts' many of the underlying points made should not be discounted because of the small number of patients involved and the relative short time period. We all bear a great responsibility to introduce the transplantation option or suggest referral for assessment only when there is a realistic hope of it bringing benefit. The whole aim of transplantation should be to improve the quality of life not just to extend it. It would be more honest at this relatively early stage to view it as a palliation rather than a 'cure'. Heart-lung transplantation can provide a good quality of life for an indefinite period in exchange for continuing severe symptoms and the certainty of death.

The immediate outcomes of referral are: (i) acceptance onto an immediate or active waiting list, (ii) placing on a 'holding' or provisional list (no contraindications but not yet severe enough to transplant), and (iii) non-acceptance because either the patient is too sick (preterminal) or has major physical or psychological contraindications.[3] What has not been brought out is that patients accepted onto a provisional list may experience an increase in quality of life. This is because the decision communicates two important messages to the child and family: (i) the disease is not at a stage in which death is imminent or likely to occur in the next one to two years and (ii) transplantation offers an 'insurance policy' which may be drawn on at a later date.

Certainly no family should be assessed unless heart-lung transplantation had been fully discussed at the referral centre and the problem of ignorance on the part of the family or child should not arise. Inquiries should also be made as to the family dynamics, local family support, and major medical contraindications such as advanced liver disease and previous pleurectomy in order to forestall inappropriate referrals. However, even these contraindications may change as agents such as the aprotinin (Trasylol, Bayer) make previous pleurectomy less of a problem and double lung transplantation with its improved access to the pleural cavity may enable better control of bleeding points.[8]

Assessment is bound to be stressful as issues that have been difficult to discuss within the family are brought out into the open. However, this can also be beneficial as children talk openly, often for the first time, about issues that had previously been taboo. A common theme, particularly among adolescents, is that although they knew of the severity of their condition and the risk of dying, they felt unable to talk about these fears with their parents for fear of upsetting them. Many families comment on improved motivation and more honest relationships. The presence of a transplantation programme and the fact that it is possible to restore good quality of life benefits not only the admittedly small number of children with a successful medium term outcome,[3] but also the whole population of children approaching end stage cardiopulmonary disease, letting in some hope where only inevitable deterioration and death seemed possible. This may not be an unrealistic expectation as the single largest group referred for consideration in the UK are those with cystic fibrosis. This disease accounts for approximately 30–40 deaths a year in the 5–15 year age group[4] and three to four paediatric centres could transplant something approaching this number. The problems of donor supply will remain and further improvements in controlling rejection and in identifying suitable candidates need to be made. Heart-lung transplantation and all that goes with it can certainly be stressful for health care professionals, children, and their families. The whole story cannot yet be told but an honest exposition of some of the difficulties should spur on those teams already involved to improve their procedures and alert those considering this option to the potential problems.

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See related papers on p 1018 and 1022.

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Heart-lung transplantation for cystic fibrosis. 1: Assessment

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Abstract

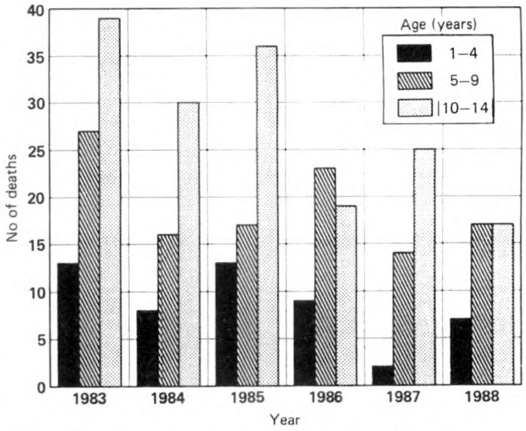
Forty five patients with cystic fibrosis (age 5–15 years) were assessed for heart-lung transplantation between September 1987 and March 1990. The two main conditions for acceptance were (i) life expectancy less than 2 years and (ii) a severely impaired quality of life. Patients were accepted onto an active waiting list (n=26), a provisional waiting list (n=15), or not accepted (n=4).

Selection was made on clinical grounds with objective measurements used as an aid in assessment. As expected, the mean values for objective measures were significantly different between patients on the active waiting list compared with the provisional waiting list/not accepted group for resting heart rate (118/minute *v* 101/minute), percentage of ideal weight (83·2% *v* 93·1%), forced expiratory volume at one second as percent of predicted normal (27·3% *v* 47·6%), Shwachman-Kulczycki score (33·6 *v* 52·5), Chrispin-Norman x ray score (25·8 *v* 22·1), 12 minute walk (540 m *v* 854 m), and minimal oxygen saturation (81·5% *v* 92%). Psychological evaluation demonstrated a 55% incidence of individual and a 50% incidence of family morbidity.

Of the 26 patients accepted onto the active waiting list, 11 have been transplanted (mean waiting time 3·3 months), 10 have died within a mean of 3·7 months of acceptance, and five remain on the active list (mean 5·6 months).

Despite the improving prognosis in cystic fibrosis[1] there is still an appreciable mortality in the young child and adolescent in the United Kingdom, with a total of 41 deaths between the ages of 1–14 years reported in 1988 (figure). Most deaths were due to respiratory disease and therefore many of these patients may be eligible for heart-lung transplantation. Heart-lung transplantation was first successfully performed in adults with pulmonary vascular disease in 1981[2] and later in those with cystic fibrosis.[3] Experience of heart-lung transplantation in children is limited, but an early report has shown encouraging results.[4]

Since paediatric referrals for heart-lung transplantation were accepted at our institutes, by far the largest single group has been children with cystic fibrosis (45 of the 64). For such a major procedure with an uncertain long term outcome, a condition for acceptance onto our programme has been a life expectancy of less than two years. However, prognostic indicators for short term survival are not available as most reports deal with long term outcome.[5–7]



Cystic fibrosis deaths, by age, in the UK for 1983–8 (supplied by the Office of Population Censuses and Surveys for England and Wales, and the Registrar General's Departments of Scotland and Northern Ireland).

Patients and methods

From September 1987 to March 1990, 45 patients with cystic fibrosis were assessed at our institutes for heart-lung transplantation. Ages ranged from 5–15 years (mean 11·3), 25 of whom were girls and 20 boys. Referred patients aged 16 years and above were assessed at our adult centre (Papworth Hospital). Before admission, referring paediatricians were requested to complete a proforma. This helped to identify those unsuitable for transplantation. Absolute contraindications were few but included previous pleurectomy and pleurodesis, advanced liver or renal disease, severe psychosocial disturbance, and high dose steroid treatment (>1 mg/kg/day). A pulmonary aspergilloma was an absolute contraindication, although allergic bronchopulmonary aspergillosis or the presence of aspergillus in the sputum were not.

Children were admitted for four to five days with their parents and, whenever possible, their siblings. They were assessed by a multidisciplinary team including carers experienced in cystic fibrosis, social worker, child psychologist and psychiatrist, and both child and family were familiarised with the full implications of heart-lung transplantation. Patients and families were also reviewed by a physiotherapist, pharmacist, and dietitian.

Each child underwent a complete clinical assessment including resting heart rate,[8] percentage of ideal weight corrected for height,[9] full lung function including plethysmography and spirometry with forced expiratory volume at one second expressed as a percentage of predicted normal ($FEV_1\%$),[10] Shwachman-Kulczycki score,[11] Chrispin-Norman *x* ray score,[12] a 12 minute walk,[13] pulse oximetry (Ohmeda Biox 3700), and assessment of right heart function by electrocardiography and echocardiography.[14]

Renal function was assessed by plasma urea and creatinine estimation together with a measurement of glomerular filtration rate (24 hour creatinine clearance or radiolabelled EDTA estimation of glomerular filtration rate). Hepatic function was assessed by liver ultrasonography together with liver function tests and coagulation studies. Liver biopsies were not routinely performed.

Microbiological investigations of sputum and throat and nose swabs were performed in order to ensure appropriate chemoprophylaxis at the time of transplantation. Surveillance for active mycobacterial infection was also performed. Urine was collected for bacterial and viral culture together with serum titres for cytomegalovirus, toxoplasma, hepatitis B surface antigen, HIV, herpes simplex virus, varicella zoster virus, Epstein-Barr virus, rubella and measles viruses. Fungal titres for candida and aspergillus fumigatus were also performed. These provided valuable baseline data for clinical management during postoperative immunosuppression.

Complete dental examination, including radiography, was undertaken to exclude occult infection and any dental caries found was dealt with during or soon after admission.

As well as a formal 12 lead electrocardiography and echocardiography, a 24 hour electrocardiographic tape was taken to assess the suitability of the heart as a possible donor organ (the domino procedure).[15]

Both patient and family underwent extensive psychosocial evaluation by a psychiatrist (BL) and psychologist (ES). This was complemented by informal assessment throughout the admission by the transplant liaison sister (MG).

The child's psychological functioning was determined by his/her mental state (mood, anxiety), coping mechanism, and general adjustment and attitude to illness. Questionnaires and a semistructured psychiatric interview were utilised. Three levels of functioning were determined: level 1 indicated normal functioning, level 2 moderate dysfunction, and level 3 severe dysfunction.[16] A similar rating of functioning of the family as a whole was obtained by observing family interactions, parental subsystem, communication, and problem solving during a clinical interview.

On completion of the inpatient assessment, a combined decision meeting was convened with the family. For younger children (less than 10 years), this was usually confined to the parents, but older children were included if they wished. Patients were either accepted on to an active transplant waiting list indicating they were eligible for transplantation from that time, a provisional waiting list indicating that they were not severely enough affected but would be reassessed at a later date, or not accepted having been assessed as too well.

Children accepted on to the active list underwent further preparation by the ward sister, the transplant liaison sister, the play specialist and/or school teacher. Logistical arrangements for patient transfer at time of transplantation, including the issuing of a long range radio pager, were organised by the coördinator (IM).

Comparison of clinical measurements of those accepted and on those not accepted to the active waiting list was performed. Statistical analysis was by Student's *t* test for unpaired data. A p value of less than 0·05 was accepted as significant.

Results

Of the 45 patients assessed, 26 were accepted on an active waiting list, 15 on a provisional waiting list, and four were not accepted.

Mean (SD) values of heart rate, percentage of ideal weight corrected for height, $FEV_1\%$, minimal oxygen saturation, distance covered in a 12 mintute walk, Shwachman-Kulczycki score and Chrispin-Norman score of the two groups (active waiting list and provisional waiting list/not accepted group) are shown in table 1. Significant differences were noted when comparing all measurements of these two groups.

Levels of psychosocial functioning of 22 children and families accepted on the active waiting list are shown in table 2. No patients were refused acceptance onto the transplantation programme for psychological reasons, although one patient underwent two months further treatment before being placed onto the active transplant list. The four remaining children at level 3 were referred for further psychological treatment but were *not* excluded from acceptance on the active waiting list.

Table 1 Mean (SD) values of clinical measurements in patients on active waiting list and provisional waiting list/not accepted group

Measurement	*Active waiting list (n=26)*	*Provisional waiting list/ not accepted (n=19)*	*p Value*
Heart rate (beats/minute)	118 (14)	101 (9)	<0·001
% Ideal weight	83·2 (9·7)	93·1 (9·3)	<0·01
$FEV_1\%$	27·3 (10·5)	47·6 (21·2)	<0·001
Shwachman-Kulczycki score	33·6 (4·9)	52·5 (7·8)	<0·001
Chrispin-Norman chest *x* ray score	25·8 (2·5)	22·1 (3·2)	<0·001
12 Minute walk (m)	540 (324)	854 (235)	<0·01
Minimal oxygen saturation (%)	81·5 (9·6)	92 (3·9)	<0·001

Comparison between groups by Student's *t* test (significance level p<0·05).

Table 2 Level of psychosocial functioning of 22 individual children and whole families accepted onto the active waiting list for heart-lung transplantation

	Level 1 (normal function)	*Level 2 (moderate dysfunction)*	*Level 3 (severe dysfunction)*
Child (n=22)	10	7	5
Family (n=22)	11	8	3

Only one patient had clinical evidence of severe hepatic involvement associated with portal hypertension. None of the patients assessed showed abnormal renal function. Mean (SD) plasma creatinine concentration was 49·4 (7·35) μmol/l. All patients on the active list were negative for cytomegalovirus antibody. This had important implications for donor selection, as we specified cytomegalovirus compatibility in order to avoid the development of life threatening pneumonitis post-transplant.[17]

Of the 26 patients accepted on the active waiting list, 11 were transplanted (mean waiting time 3·3 months), 10 died within a mean of 3·7 months of acceptance, and five remain on the active list (mean 5·6 months).

Discussion

One of the major difficulties confronting any new transplantation programme is the determination of appropriate and practical selection criteria for recipients. We chose a prognosis of less than two years as the current survival figures for heart-lung transplantation seen in the adult series over this period was 70%.[18] The lack of information on short term prognosis in cystic fibrosis therefore compromised this selection criterion.

The selection criteria were supported by the fact that all deaths occurring on the active waiting list were within our prognostic time scale and none of those suriviving on the list untransplanted have so far exceeded this two year period. On the other hand, of the patients on either the provisional waiting list or those not accepted, only one death occurred. This was due to an unexpected viral pneumonia in a 7 year old boy with a baseline Shwachman-Kulczycki score of 49. It is our practice to reassess all patients on the provisional waiting list at intervals of three to 12 months and place them on the active list if continuing clinical deterioration is observed. However, it is likely that a small number of children on the provisional list may die after a sudden unexpected intercurrent illness as occurred in this patient.

We found the most helpful clinical measures in determining short term prognosis, and therefore selection for transplantation, were percentage of ideal weight, FEV_1%, Shwachman-Kulczycki score, and lowest oxygen saturation obtained obtained during a 12 minute walk. Although it is impossible at present to give absolute 'cut off' parameters, the values shown in table 1 give objective guidelines of severity to referring clinicians when considering transplantation in the deteriorating child with cystic fibrosis. Longer term follow up of survival of those patients assessed may yield more concrete guidelines.

The second part of our selection criteria, namely a severely impaired quality of life, raises further difficulties. Few guidelines are available in the current literature[19] and the whole topic is plagued by subjective interpretations. By combining both objective clinical measurements and the more subjective quality of life measures, we believe an appropriate decision can be made.

Contraindications to heart-lung transplantation are decreasing in number as further experience is gained. For example, patients with previuos thoracotomy, diabetes mellitus, and those on low dose steroid treatment are now accepted. Those with cirrhosis and portal hypertension may also be eligible for heart, lung, and liver transplantation as experience with this technique increases.[20] Accordingly, current absolute contraindications may become only relative in the future.

We were fortunate in that patients, and/or families, who would be unsuitable for heart-lung transplantation due to psychosocial contraindications, tended not to be referred for assessment in the first instance. However, there remains a relatively high incidence of psychological morbidity in those reaching formal assessment as observed in our population. Indentifying the child and/or family with underlying psychological problems (level of functioning 2 and 3) helps to establish a framework for preparation for transplantation and after care. Together with the added burdens of awaiting transplantation and then of transplantation itself,[21] it is imperative that a psychosocial support network is mobilised for 'at risk' patients and families.

Dispelling unrealistic expectations and confronting families with the realities of transplantation can be painful, but is an essential part of the assessment. The uncertainties of the waiting period, the immediate postoperative phase, and more importantly the long term issues of rejection, infection, life long drug treatment with its associated side effects, repeated hospitalisation and disruption to the family, must be balanced against the hoped for improved quality of life. The same degree of honesty must be afforded the child, particularly in confronting death, something many parents find difficult to cope with.

At the time of preparation, the total cost of the assessment admission was £1408. This represented 5·4% of the first year's total cost when transplantation was performed. This cost could be greatly reduced if assessment was managed on an outpatient basis, but we feel this approach would be counterproductive for both the patient and the transplant team.

The outcome of those patients undergoing heart-lung transplantation is discussed in the second part of this review.[22]

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See related papers on p 1013 and 1022.

Endotoxin antibody in the treatment of Gram negative septicaemia

Advances in the understanding of mechanisms of pathogenesis in severe sepsis (see Archivist 1991: 137 and 340) have led to fresh thoughts about possible treatments. A recent paper in the *New England Journal of Medicine* (Ziegler *et al*, 1991; **324**: 429–36) describes the results of giving human monoclonal antibody against endotoxin to adults with Gram negative bacteraemia and septic shock.

The release of endotoxin into the circulation leads to shock and tissue damage through the intermediary of cytokines. The destruction of endotoxin might therefore be expected to be beneficial. Previous trials showing a protective effect have involved the use of polyclonal antisera produced in human volunteers. Monoclonal IgM antibody (HA-1A) is produced from myeloma cell cultures. It is more specific, binding to the lipid A domain of the lipopolysaccharide endotoxin, and its use avoids the need to immunise volunteers and the dangers of using pooled human blood.

The trial was performed at 24 academic medical centres in the United States, Canada, and Europe. All the patients were severely ill with septic shock defined on clinical grounds.

A total of 543 patients entered the trial and were randomly assigned to receive either HA-1A or placebo (human albumin). Two hundred patients proved to have Gram negative bacteraemia on blood culture and the analysis of the trial results is confined to this 200, 105 of whom received HA-1A and 95 placebo.

Overall mortality was reduced from 50% in the placebo group to 30% in the treatment group. Benefit was seen both in those very severely ill (severe shock and high APACHE score) and in those less severely ill. No serious adverse reactions to the treatment were encountered.

This trial on adults has important implications in paediatrics. *Neisseria meningitidis* is a potent producer of endotoxin and antibody against lipid A should be effective in meningococcal septicaemia. A multicentre trial of HA-1A in meningococcal septicaemia in children has recently started. The results will be awaited with great interest.

ARCHIVIST

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Heart-lung transplantation for cystic fibrosis. 2: Outcome

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Abstract

From March 1988 to March 1990, 11 children with cystic fibrosis (age 5–15 years) underwent combined heart-lung transplantation at our institutes. Maintenance immunosupression consisted of cyclosporin and azathioprine with corticosteroids and antithymocyte globulin used perioperatively and during rejection episodes. Six patients (55%) survive from 1·5–23 months all of whom have improved life quality. Actuarial survival to 1 year was 55%. At six months after transplant, mean forced expiratory volume at one second was 73·5% of predicted normal, compared with 25% before transplant. There was one perioperative death, three later deaths associated with obliterative bronchiolitis at two, eight, and nine months, and one from mediastinitis at four months. Of the 15 children accepted for transplantation but not receiving grafts, 10 have died (eight within four months of being placed onto the transplant list).

Early postoperative problems included acute reversible rejection (n=10), meconium ileus equivalent (n=3), and pancreatitis (n=1). There was a high incidence of later pulmonary rejection with a mean of 5·7 episodes per patient in the first six months. Pulmonary infection occurred relatively infrequently, with *Pseudomonas aeruginosa* being the most common pathogen. Persistent diabetes mellitus requiring insulin occurred in four and systemic hypertension developed in one.

Heart-lung transplantation has been successfully used in the management of end stage respiratory disease in adults with cystic fibrosis.[1] The early fears of disease recurrence and overwhelming sepsis in those transplanted have been allayed.[2] This has encouraged the referral of paediatric patients with cystic fibrosis, who currently represent the largest group being assessed for transplantation at our institutes.[3] We have described our experience with the assessment of patients referred for heart-lung transplantation in the first part of this review[4] and now detail outcome in those transplanted.

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Patients and methods

From March 1988 to March 1990, 11 children with cystic fibrosis (age 5–15 years, mean=12) including six boys and five girls, underwent combined heart-lung transplantation. Ten were performed at the Hospital for Sick Children, London and one at Papworth Hospital, Cambridge. All patients were severely incapacitated with end stage lung disease with a mean (SD) forced expiratory volume at one second as percentage of predicted normal (FEV_1%) of 25·0 (10·5). They all had a poor quality of life with a mean (SD) Shwachman-Kulczycki score of 33·3 (4·3) (table 1).

Donor organs were obtained from ABO blood group and cytomegalovirus antibody compatible patients who had sustained brain death. Size matching was by predicted donor total lung capacity together with direct comparison of chest radiographs of donor and recipient. Organ evaluation and procurement were performed as previously described.[5] The recipient operation[6] was timed to minimise total organ ischaemia to 240 minutes.

Perioperative immunosuppression comprised cyclosporin, azathioprine, corticosteroids, and antithymocyte globulin (Atgam-Upjohn or Lymphoglobuline-Merieux) (table 2). Maintenance treatment was with cyclosporin to achieve whole blood concentrations of 600–1000 μg/l (modified fluorescence polarisation assay, TDx method, Abbott Laboratories) and azathioprine (ensuring total white cell count did not fall

Table 1 Details of patients with cystic fibrosis receiving heart-lung transplantation

Patient No	*Age (years)*	*Sex*	*Preoperative FEV_1%*	*Preoperative Shwachman-Kulczycki score*	*Waiting period (days)*	*Ischaemic time (min)*	*Postoperative ventilation (hours)*
1	11·5	F	15	NA	170	184	6
2	14·0	F	21	30	13	170	64
3	14·3	M	18	32	143	170	28
4	13·2	M	25	27	7	250	7
5	9·7	M	19	35	174	170	19
6	5·8	F	15	34	34	98	14
7	8·1	F	38	42	230	210	36
8	14·2	M	31	36	73	239	27
9	11·9	M	39	36	59	151	14
10	14·3	F	43	34	85	96	8
11	15·3	M	11	27	54	204	102
Mean	12·0		25·0	33·3	98·8	176·5	29·5

NA, not applicable.

Table 2 Immunosuppression for heart-lung transplantation in cystic fibrosis

	Preoperative	*Perioperative*	*Postoperative*
Cyclosporin*	5–10 mg/kg	—	5–50 mg/kg/day
Azathioprine	2 mg/kg	2 mg/kg/day	0·5–2 mg/kg/day†
Methylprednisolone (intravenous)		10 mg/kg×2 2 mg/kg×3	For rejection (10 mg/kg×3)
Antithymocyte globulin	—	0·5 ml/kg×3‡	For rejection
Oral prednisolone	—	—	For rejection (1 mg/kg/day and reducing)

*Cyclosporin administered via enteral route, together with pancreatic enzymes, three times daily.
†Dose adjusted to keep white cell count $>5\times10^9$/l.
‡Dose adjusted according to total T cell number.

below $5{\cdot}0\times10^9$/l). Corticosteroids were given during acute rejection episodes commencing with three daily doses of intravenous methylprednisolone (10 mg/kg/dose) followed by a reducing oral prednisolone course (starting at 1 mg/kg/day).

Initial postoperative management included early extubation and maintenance of a negative crystalloid fluid balance to prevent pulmonary oedema. Histamine (H_2) receptor antagonists (ranitidine 4 mg/kg/day) and oral antacids were administered until full enteral feeding was achieved. Regular oral acetylcysteine (Fabrol sachets, Zyma), lactulose, and pancreatic enzymes (Pancrex V powder, Paines and Byrne or Creon capsules, Duphar) were given, the latter with both food and cyclosporin. If enteral energy intake was poor (less than 0·42 MJ/kg/day) by three to four days postoperatively, intravenous feeding was instigated.

Perioperative antibiotic prophylaxis consisted of flucloxacillin (100 mg/kg/day) together with either cefotaxime (100 mg/kg/day) or gentamicin (4 mg/kg/day with the dose adjusted to blood concentrations and renal function). In addition, appropriate antipseudomonal antibiotics (for example, ceftazidime 150 mg/kg/day) were administered for five to seven days if this organism had been grown from the excised trachea. Co-trimoxazole (sulphamethoxazole 20 mg and trimethoprim 4 mg/kg/day) was given after the first week as prophylaxis against *Pneumocystis carinii* pneumonitis.[7] If there was a history of recurrent herpes simplex virus infection or the patient was herpes simplex virus antibody positive, acyclovir (200 mg/m²/8 hours) was administered over the first three postoperative months. An antifungal agent (nystatin suspension 100 000 units four times a day) was continued indefinitely.

Surveillance for pulmonary rejection and/or infection was by regular clinical examination, chest radiography,[8] spirometry,[9] and when indicated, transbronchial biopsy.[10] [11] Patients were given portable microspirometers (Micro Medical) and twice daily FEV_1 and forced vital capacity measurements were recorded. If there was a fall in these values of greater than 10–15%, bronchoscopy, bronchoalveolar lavage, and transbronchial biopsies were performed. Bronchoalveolar lavage was used for bacterial and viral culture, and histopathological examination for evidence of rejection was performed on the transbronchial biopsy specimen.[12] A single biospy sample was also sent to culture for opportunistic organisms. If rejection was present histologically, steroids were administered as above. Infections were treated according to culture.

Patients were discharged with their parents and siblings to a nearby family hostel after three to four weeks, where they remained for a further one to two weeks before their return home. Outpatient follow up was once a week for three months, twice a week to six months, and every three to four weeks thereafter. This included clinical assessment together with weight, blood pressure, urinalysis, and chest radiography being performed. Full blood count, concentrations of serum urea, electrolytes, creatinine, C reactive protein, cyclosporin, and liver function tests were routinely performed. Immunosuppression treatment was altered according to these results. Systemic hypertension was treated by calcium channel blockers (nifedipine 1–4 mg/kg/day). Persistent hyperglycaemia was managed with a twice daily regimen of insulin incorporating short and longer acting forms (Actrapid and Monotard, Novo Laboratories Ltd).

Results

The mean waiting period from acceptance onto the active waiting list to transplantation was 98·8 days (range 7–230 days). All grafts were procured distantly. Total mean (SD) organ ischaemic time was 176·5 (47·4) minutes. Early graft function was good in all except patient 7. Ventilatory support was required for a mean of 29·5 hours (range 6–102 hours) and all survivors were breathing spontaneously in air by the end of the first postoperative week (table 1).

Of the 11 children who have received heart-lung transplantation, six (55%) survive from 1·5–23 months, all of whom have returned to age appropriate activities (fig 1). Although our

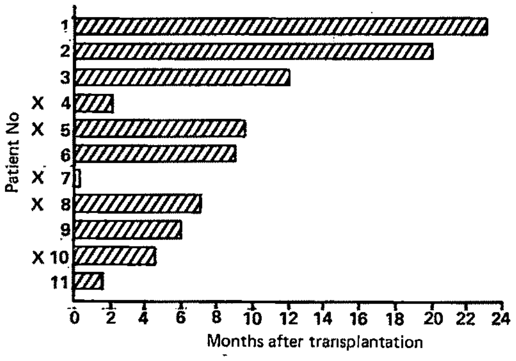

Figure 1 Survival in months of 11 patients with cystic fibrosis after heart-lung transplantation. Patients who have died are indicated by a cross.

numbers were small and follow up limited, the actuarial survival to one year was 55% (Cutler-Ederer method). There were five deaths. The first (patient 4) occurred at 69 days from chronic pulmonary rejection associated with respiratory infections caused by *Pseudomonas aeruginosa*, *Mycoplasma pneumoniae*, and adenovirus. Postmortem examination of the lungs revealed obliterative bronchiolitis. The second death (patient 7) occurred at 36 hours postoperatively. This appeared to be associated with donor/recipient lung size mismatch. The smaller implanted lungs became overinflated which produced increased pulmonary vascular resistance and subsequent right heart failure. Patients 5 and 8 died at 291 and 242 days postoperatively respectively. Obliterative bronchiolitis was diagnosed in both at postmortem examination. The final death was patient 10 as a result of mediastinitis and the development of an aortic pseudoaneurysm.

Early acute pulmonary rejection, diagnosed either clinically or histologically, occurred in two patients (patients 2 and 11) during the first week, and in the surviving patients during the second week after transplantation. All were treated with intravenous boluses of methylprednisolone and showed resolution of clinical and radiological signs. Subsequent rejection episodes diagnosed histologically by transbronchial biopsy specimens were frequent. There was a mean of 5·7 episodes of rejection per patient in the seven surviving the first six months after transplant (fig 2).

Excluding the early postoperative period when antimicrobial prophylaxis was given, a total of 14 microbiologically proved and treated pulmonary infective complications, including tracheobronchitis in 12 and pneumonia in two, occurred in those seven patients surviving the first six months. These often accompanied rejection episodes (fig 2). This represented a mean incidence of 2·0 respiratory infections per patient in the first six months. The most common pathogen isolated was *P aeruginosa* (9/14) and *Staphylococcus aureus* and group A β haemolytic streptococcus were also cultured. Adenovirus and *M pneumoniae* were implicated on serological evidence (fourfold rise in titres) in producing a severe pneumonitis in patient 4.

Other infective events included herpes simplex labialis in three patients. Chronic mediastinitis due to *P aeruginosa* associated with the development of an aortic pseudoaneurysm occurred in patient 10. Death resulted from neurological complications after resection of the aortic pseudoaneurysm. Cellulitis of the dorsum of the foot subsequent to an infected toe also developed in this patient.

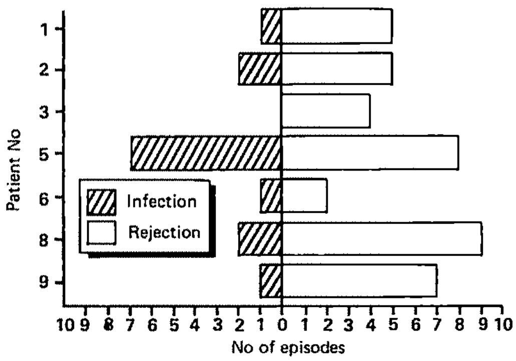

Figure 2 Number of episodes of pulmonary rejection and pulmonary infection in those cystic fibrosis patients surviving the first six months after heart-lung transplantation.

Other early complications included meconium ileus equivalent, defined as subacute gastrointestinal obstruction due to inspissated faeces, which occurred in three patients (patients 2, 3, 4). This responded to medical treatment with oral acetylcysteine, aperients, and Gastrografin enemas (Schering). In the later patients in the series, prophylactic treatment with acetylcysteine was started in the perioperative period when bowel sounds were audible and continued until a regular bowel pattern was established. Pancreatitis occurred in one patient (patient 8) on day 3. This was successfully managed conservatively by gut rest and the implementation of parenteral nutrition.

Later problems included the development of diabetes mellitus subsequent to corticosteroid treatment. This occurred transiently in two patients (patients 1 and 5) and four (patients 2, 4, 8, 10) required long term treatment with insulin.

Tracheal stenosis developed in two patients

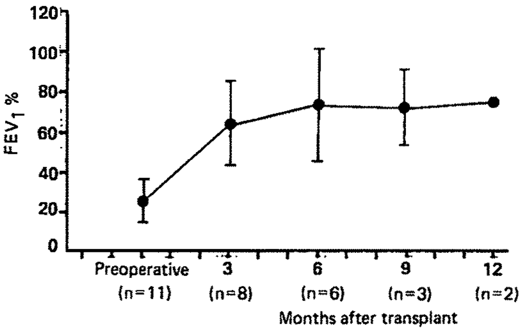

Figure 3 Mean (SD) FEV₁% in patients with cystic fibrosis patients, preoperatively and to 12 months after heart-lung transplantation. The number of patients in each epoch is indicated.

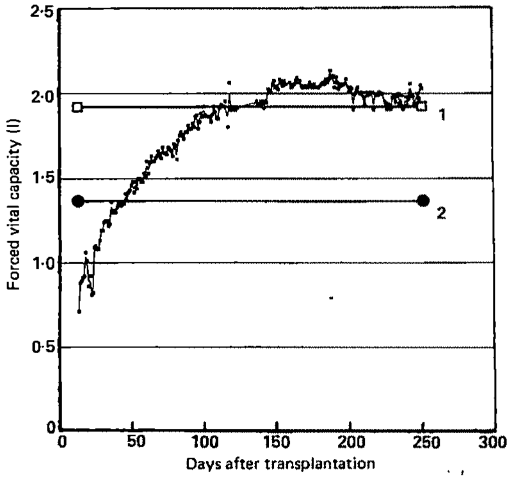

Figure 4 Forced vital capacity of patient 2 after heart-lung transplantation. Note the increase to recipient predicted values (line 1) rather than those predicted for the donor (line 2).

(patients 5 and 8). This developed just below the tracheal anastomosis at six and three months respectively. They were successfully managed by tracheal dilatation and insertion of silastic endotracheal stents.[13]

Systemic hypertension requiring treatment developed in only one (patient 8) and was successfully controlled with the calcium channel blocker, nifedipine (1 mg/kg/day).

Lung function after transplant, measured by $FEV_1\%$, showed an increase in all patients who survived beyond hospital discharge, with a mean of 73·5% at 6 months (fig 3). Lung function after transplant, measured by forced vital capacity, appeared to follow that predicted for the recipient rather than the donor (fig 4).

Discussion

The early postoperative results in our series were encouraging, with only two patients not surviving to hospital discharge. Excellent early graft function in all but one patient (patient 7) affirmed our donor selection and procurement methodology.[14] Of more concern was the morbidity and mortality specifically associated with the high incidence of pulmonary rejection with or without associated respiratory infection. This appeared to lead to definite obliterative bronchiolitis in three (patients 4, 5, and 8, which was confirmed at postmortem examination) and chronic rejection changes in two (patients 1 and 2) despite augmented immunosuppression.[15,16] The increased episodes of rejection do not appear related to the pre-existing diagnosis, as adult recipients of heart-lung transplants with cystic fibrosis do not reject any more frequently than adult patients without cystic fibrosis.[17]

Although Bailey *et al* have noted less rejection in young infants receiving orthotopic cardiac transplants,[18] we have noted an *increased* incidence in the child receiving a combined heart-lung graft compared with the adult, using a similar immunosuppression and monitoring regime.[19] This discrepancy remains unexplained.

Pulmonary infection often coexisted with rejection though did occur de novo. The high percentage of *Pseudomonas* spp isolated reflects the prevalence of this organism in patients with cystic fibrosis. The source appears to be the colonised native upper airways. Although often cultured from the respiratory tract, the majority of infections involved the tracheobronchial tree rather than the lung parenchyma. In the adult series the incidence of true pneumonia with this organism is not significantly different between recipients of heart-lung transplants with and without cystic fibrosis.[17]

The introduction of bronchoscopy, both flexible fibreoptic and rigid, bronchoalveolar lavage, and transbronchial biopsy in the management of our paediatric patients[11] has been of great value in assessing pulmonary infection and rejection. However, these procedures are more hazardous in children and we therefore routinely use general anaesthesia and fluoroscopy to decrease the risk of complications (for example, hypoxia subsequent to a compromised airway and pneumothorax).

Pancreatitis was a clinical problem in patient 8. No infective cause was found and he responded to conservative medical management. This has been previously described occurring in adult cardiac and cardiopulmonary recipients.[20] Considering the degree of pancreatic involvement in cystic fibrosis, it is surprising that more cases were not seen. This is particularly true in view of the high incidence of diabetes mellitus observed (6/11). This latter problem is a well known complication of cystic fibrosis,[21] but was undoubtedly exacerbated by the high dose corticosteroids used for treatment of graft rejection.

There was a higher incidence of tracheal anastomotic stenosis (two of 11 patients 18%), then observed in the adult series, despite identical operating techniques. This may be explained by a less well developed coronary-bronchial collateral circulation in the younger patient.[22] Other paediatric series have experienced an increased incidence of this complication.[23] It was of interest to note that both affected children rapidly succumbed to obliterative bronchiolitis after repeated episodes of acute allograft rejection.

Although our short term survival figures for heart-lung transplantation in cystic fibrosis compared with the current worldwide one year survival of 61%,[24] they remain lower than the Papworth Hospital adult series.[1] This may be related to a greater propensity to severe graft rejection in the child, though our numbers remain too small to make confident statistical comparisons regarding this. Certainly, it seems greater control of graft rejection with improved methods of immunosuppression are required to improve the overall longer term results.

We would like to thank Mr P Goldstraw, Brompton Hospital, London, for treating our patients with tracheal stenosis and special thanks to Miss P Smith and Miss L Stanger for preparation of the manuscipt.

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Commentary

These two papers from the Hospital for Sick Children and Papworth Hospital give a very clear outline of their meticulous multidisciplinary team approach to the assessment of children with cystic fibrosis being considered for heart-lung transplantation. The survival of 55%, three months to three years after transplantation, is disappointing compared with the adult figures from Papworth, presented recently, of 78% at one year and 66% at 3 years (Cystic Fibrosis Research Trust Meeting, 1991). My experience at the Brompton Hospital was broadly similar to that of the Hospital for Sick Children, though more of my patients were not accepted on the programme and consequently a large percentage on the active waiting list were actually transplanted.

Whitehead and colleagues have attempted to define the indices of poor short term survival based on deaths in their cystic fibrosis clinic over a 10 year period but fail to indicate how many patients with similar prognostic features survived for more than two years. Furthermore, they do not define the features which indicate that it is too late to consider heart-lung transplantation. The mean time to death of their 10 patients who died awaiting transplantation was only 3·7 months, suggesting that selection should be based not only on a maximum projected survival of two years without heart-lung transplantation but also a minimum of three months. This might avoid some of the inevitable anguish, recrimination, and guilt suffered by the families of those who die waiting.

See related papers on p 1013 and 1018.

From the combined figures from the Brompton Hospital and Hospital for Sick Children only a sixth of the referrals had truly benefited from heart-lung transplantation, half had died either before or after the procedure, and the remainder were still waiting. These are the harsh realities which paediatricians must now present to their patients with cystic fibrosis and families, but there are additional less well defined issues which must also be considered.

The psychosocial problems which occur in those families drawn into the transplantation programme are immense. For some the hope generated has a very positive effect but for many the whole procedure is a nightmare which ends in disaster. Heart-lung transplantation is not the miraculous cure imagined by many. It merely replaces lungs diseased by cystic fibrosis with a foreign heart and lungs at perpetual risk of rejection and an inevitable iatrogenic immunodeficiency. Even if the results improve substantially, there will never be enough hearts and lungs available for all but a minority of patients. Indeed if all patients with cystic fibrosis deemed suitable for heart-lung transplantation were referred to transplant centres, in addition to the vast number of patients with other heart and lung diseases, then the percentage achieving benefit would be tiny.

The spectre of heart-lung transplantation has already affected our practice in cystic fibrosis clinics, forestalling the well established use of pleurectomy for pneumothoraces, steroids in end stage disease, and effective terminal care. Such changes must be resisted at all costs and heart-lung transplantation should not deter continuing effort to control cystic fibrosis medically.

Can the benefit from the massive investment in heart-lung transplantation for a lucky minority really offset the suffering of the majority? This issue is far from resolution and open discussion in the journals is essential to allow us all to reach an informed opinion.

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Olivopontocerebellar atrophy of neonatal onset and disialotransferrin developmental deficiency syndrome

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Abstract

Two brothers presented with olivopontocerebellar atrophy of neonatal onset. The clinical features (failure to thrive, hypotonia, liver disease, effusions, and visual inattention) were similar to those of the four cases already reported, as were the necropsy findings of olivopontocerebellar atrophy, hepatic steatosis and fibrosis, and microcystic renal changes. The clinical similarities between this and the disialotransferrin developmental deficiency syndrome were noted. The characteristic abnormality of serum transferrin found in the latter syndrome was also found in the two cases reported here.

We suggest that both syndromes are caused by the same, or related, defects in glycoprotein metabolism.

During the past five years, four children from two separate families have been described who had olivopontocerebellar atrophy of neonatal onset.[1 2] The olivopontocerebellar atrophy seems to be just one manifestation of a congenital multisystem disorder that affects brain, liver, kidney, retina, and joints in particular, and which seems to have an autosomal recessive inheritance.

The diagnosis of olivopontocerebellar atrophy rests primarily on morphological evidence of degeneration of the cerebellar cortex and its afferent pathways; it has been well described in adults and to a lesser extent in older children. The first cases in adults were described at the turn of the century.[3 4] In 1970, Konigsmark and Weiner classified it into five types, type II being of recessive or sporadic inheritance, the other types being autosomal dominant.[5] It is now generally accepted that it is not a single disease, but is the result of a number of clinically and genetically separate conditions.

The first report of neonatal onset olivopontocerebellar atrophy with systemic features was by Agamanolis *et al* in 1986. They described a brother and sister with the condition and suggested that it may have been caused by a primary lipoprotein disorder.[1] Harding *et al*, two years later, noticed low serum concentrations of thyroid binding globulin and caeruloplasmin in the two cases that they reported, thus raising the possibility of an abnormality of glycoproteins, although this was not formally stated in their paper.[2]

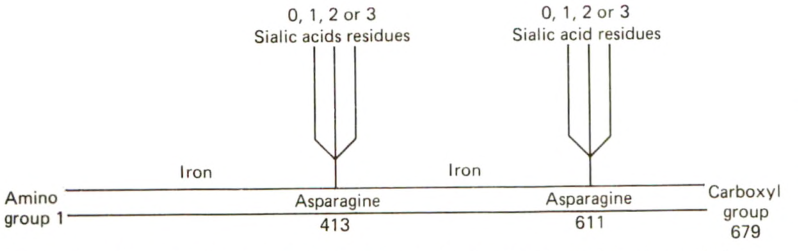

Figure 1 Diagram of human transferrin molecule showing positions of the glycan chains, each of which may have 0–3 sialic acid residues attached. The protein is divided into two domains, Nt and Ct, each of which can bind one ferric ion.

A less severe disorder has been described in recent years with many features in common with olivopontocerebellar atrophy of neonatal onset including failure to thrive, developmental delay, hypotonia, retinal abnormalities, liver disease, joint restrictions, pericardial effusions, and cerebellar hypoplasia or atrophy. This has been named disialotransferrin developmental deficiency (DDD) syndrome[6] or carbohydrate deficient glycoprotein syndrome.[7]

Abnormalities of glycoproteins have been found in patients with DDD syndrome,[6–10] the most specific biochemical marker being an alteration in the glycosylation pattern of serum transferrin.[6 10] Transferrin is one of the main serum glycoproteins that transport iron, and it has two N linked glycosylation sites (fig 1). Separation of transferrins in clinical samples by isoelectric focusing may resolve up to seven transferrin bands containing between 0 and 6 sialic acid residues.[11] In normal serum, transferrin with four sialic acid residues (tetrasialotransferrin) predominates, but in serum from patients with DDD syndrome there is a pronounced reduction in tetrasialotransferrin and a corresponding increase in components containing 0 and 2 sialic acid residues (asialotransferrin and disialotransferrin).[6 10]

In view of the clear clinical similarities between neonatal onset olivopontocerebellar atrophy and DDD syndrome it is important to look for abnormalities in serum glycoproteins in cases of olivopontocerebellar atrophy of neonatal onset.[12] We report two further cases in which plasma transferrin that is deficient in sialic acid has been specifically sought.

Case reports, subjects, and methods

CASE REPORTS

Case 1

This boy was the third child of unrelated white parents who already had two daughters who were entirely well. He was born at 37 weeks' gestation, after presenting in a double footling position. The pregnancy had been uneventful. He weighed 2800 g at birth, and Apgar scores were 3 at 1 minute and 10 at 5 minutes. Because of some floppiness and grunting the infant was admitted to the special care baby unit but settled rapidly and was soon established on full breast feeding. It was noted, however, that he had a relatively large head circumference (38 cm, >90th centile), puffy feet, and limited abduction of the hips. His chromosomes were therefore checked and found to be normal male (46XY). Despite feeding well at home he failed to thrive and at the age of 6 weeks some facial oedema was noticed. He smiled at 7–8 weeks but showed little sign of visual fixation, and no head control. At 3 months of age he was admitted to his local hospital with increasing oedema and abdominal swelling and was transferred to the Hospital for Sick Children for further investigation.

On examination he had a large head with a prominent occiput, a high forehead, an antimongoloid slant to his eyes, low set ears, and a small mandible. He had a wasted appearance with a distended abdomen, gross ascites, bilateral inguinal hernias, and moderate enlargement of the liver. His spleen was not palpable. His cardiovascular and respiratory systems seemed to be normal. He had complete visual inattention and roving eye movements, severe head lag, and truncal hypotonia. On ophthalmological examination there was optic disc pallor but no other ocular abnormality. He had restricted extension of the knees, abduction of the hips, and dorsiflexion of the ankles.

An abdominal ultrasound scan confirmed the presence of ascites and hepatomegaly. Chest radiographs, skeletal survey, and cranial ultrasound scans showed no abnormalities, but cranial computed tomograms showed dilated ventricles and subarachnoid spaces. An echocardiogram showed no pericardial effusion but suggestd some thickening of the walls of both ventricles. The electroencephalogram and electromyogram showed no abnormalities but results of the electroretinogram and visual evoked response were abnormal suggesting some alteration of function in the posterior part of the left hemisphere. The brainstem auditory evoked response suggested a significant loss of peripheral auditory function. Standard biochemical investigations showed that the serum

Table 1 Liver function tests at the time of admission to the Hospital for Sick Children

	Case No 1	*Case No 2*	*Reference range*
Total bilirubin (μmol/l)	14	<12	<17
Total protein (g/l)	29	45	61–78
Albumin (g/l)	20	24	35–55
Alanine aminotransferase (U/l)	101	64	10–35
Aspartate aminotransferase (U/l)	164	118	20–50

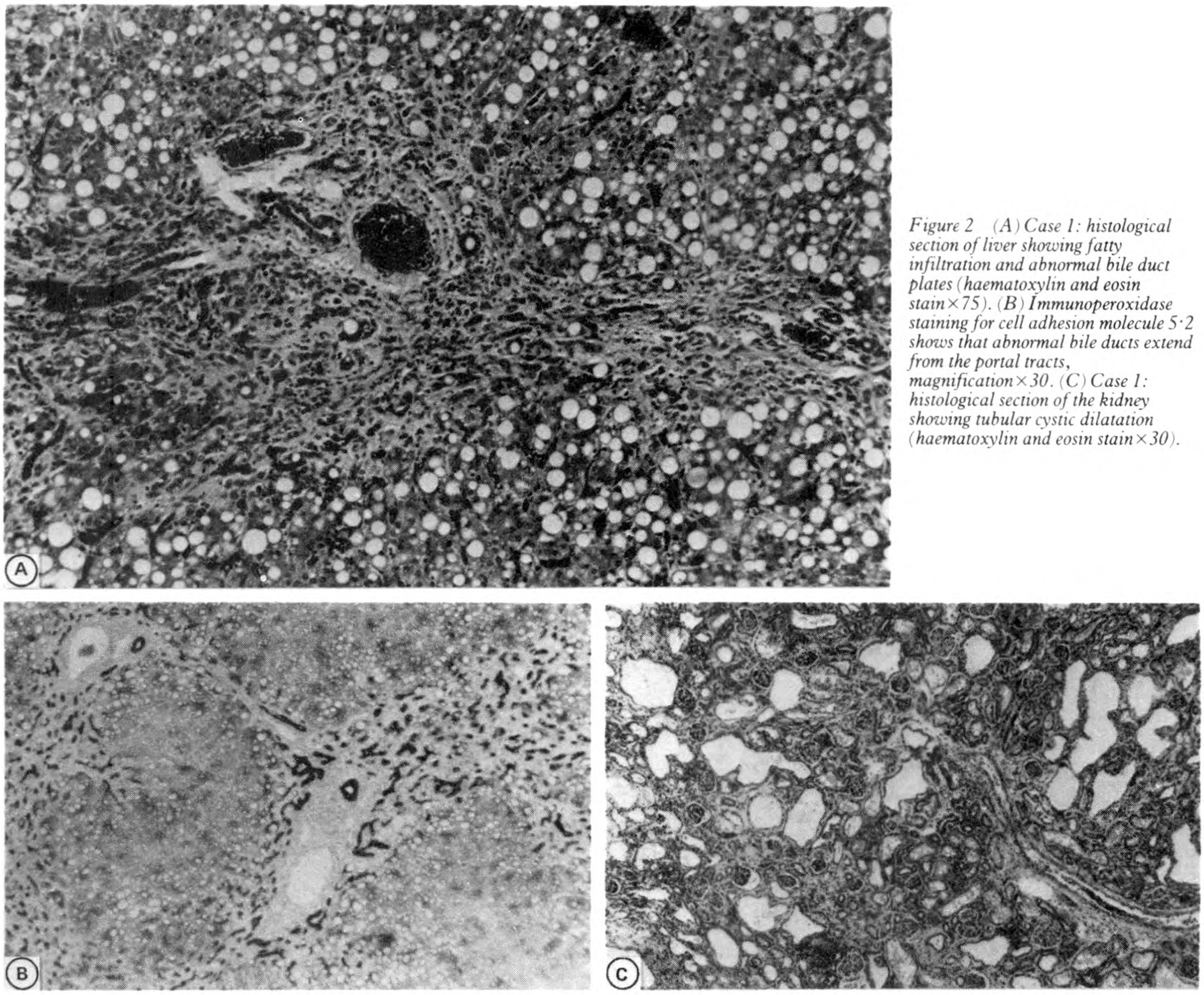

Figure 2 (A) Case 1: histological section of liver showing fatty infiltration and abnormal bile duct plates (haematoxylin and eosin stain×75). (B) Immunoperoxidase staining for cell adhesion molecule 5·2 shows that abnormal bile ducts extend from the portal tracts, magnification×30. (C) Case 1: histological section of the kidney showing tubular cystic dilatation (haematoxylin and eosin stain×30).

albumin and total protein concentrations were abnormally low, and transaminase activities were high, indicating hepatic disease (table 1). The plasma electrolyte, urea, and creatinine concentrations were within the reference range. Of the amino acid concentrations in plasma, taurine and glycine were raised. Urinary screen for organic acids, amino acids, glycosaminoglycans and reducing substances showed no abnormality. α_1-Antitrypsin concentration was just below the lower limit of the reference range at 19·2 μmol/l (20–40 μmol/l).

After treatment with diuretics and albumin his condition improved. He became oedematous again during an episode of diarrhoea, however, and required further albumin. Transfer back to the referring hospital was being arranged when he suddenly became restless with an irregular breathing pattern and died soon afterwards. He was 15 weeks old at the time of death.

Necropsy confirmed the finding of thickened ventricular walls, although no other cardiac abnormalities were discovered. The liver was enlarged and fatty and histological examination showed macrovesicular fatty change, ductal plate abnormalities, and portal fibrosis (fig 2). The kidneys were enlarged and pale; microscopically there was pronounced cystic dilatation of the tubules and collecting ducts, but the glomeruli were unaffected. The fixed brain weighed 560 g (normal for age), but the hindbrain accounted for only 18 g, 3% of the total (normal is 11% of total), the cerebellum being small with narrow prominent folia while the base of the pons was flattened (fig 3). Histological examination of the cerebellum showed subtotal loss of Purkinje cells and granule cells, and extensive depletion of the white matter accompanied by widespread gliosis, but the dentate nuclei and their outflow through the superior cerebellar peduncles were well preserved. Neuronal loss from pontine nuclei and inferior olives was severe, and the middle and inferior cerebellar peduncles and the transverse pontine fibres were extremely atrophic. Several sections of the spinal cord were normal.

Case 2

This boy was the brother of case 1 and was born just over two years later. He was delivered at term after an uneventful pregnancy. The Apgar scores were good and he weighed 2900 g at birth. In view of the previous child's history, the first examination was carried out by a consultant paediatrician, who thought he was normal. The baby fed well immediately and was discharged home 24 hours after birth.

At 4 weeks of age, however, he was referred to the Hospital for Sick Children by his general practitioner because of failure to thrive, vomiting, and abnormal eye movements. He had failed to gain any weight since birth and was now below the 3rd centile for his age. He was thin and wasted and had a prominent occiput and low set ears like his brother. Cardiovascular and respiratory systems seemed normal. His liver was palpable 1·5 cm below the costal margin and was soft and smooth. There was no ascites and no abdominal distention. Neurological examination showed general hypotonia with poor head control, roving eye movements, and

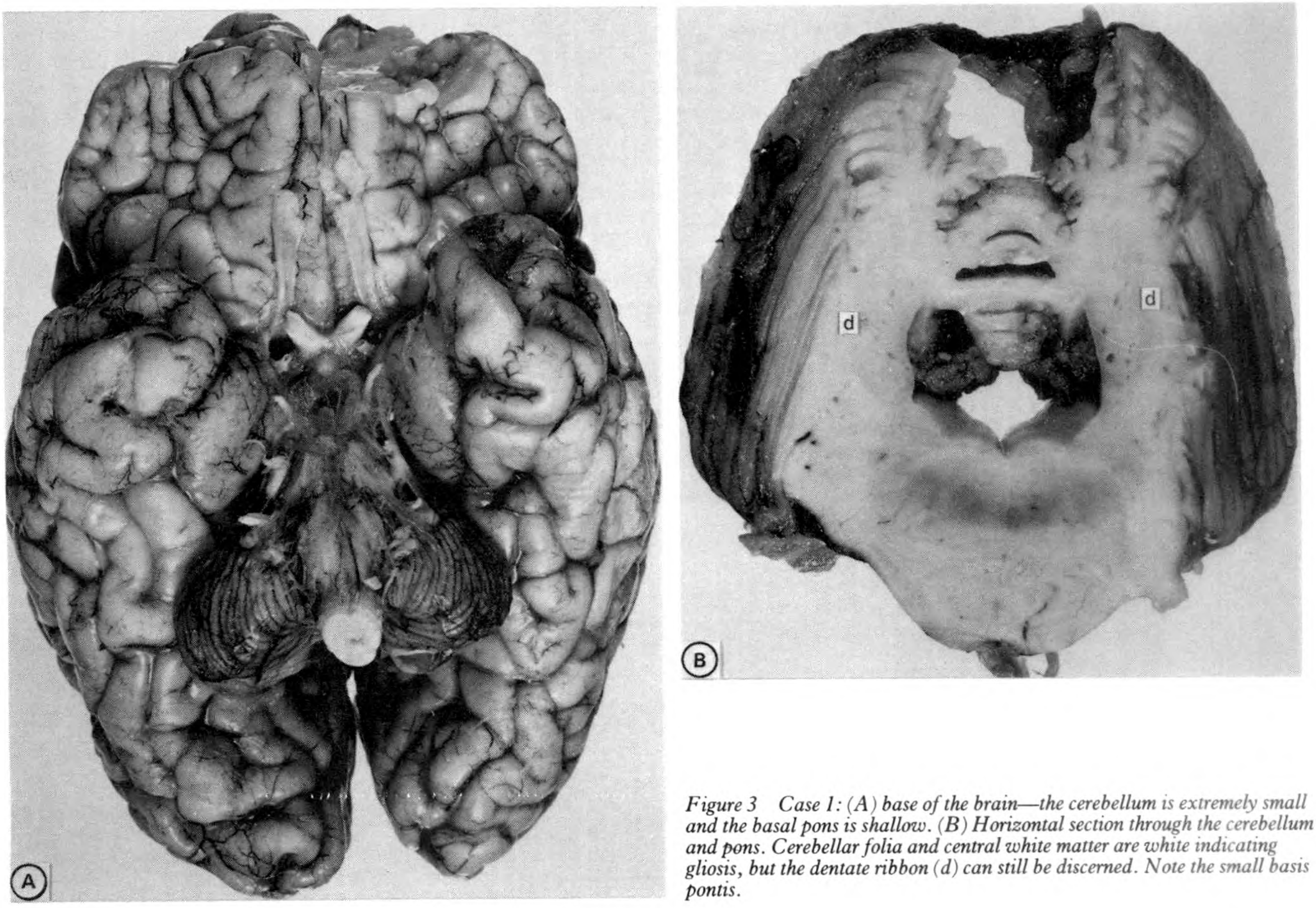

Figure 3 Case 1: (A) base of the brain—the cerebellum is extremely small and the basal pons is shallow. (B) Horizontal section through the cerebellum and pons. Cerebellar folia and central white matter are white indicating gliosis, but the dentate ribbon (d) can still be discerned. Note the small basis pontis.

no visual fixation. There was also limited abduction of both hips.

Ultrasound examinations showed a small cerebellum, a small quantity of ascites, and no abnormality of the heart. A barium swallow examination showed a sliding hiatus hernia with marked gastro-oesophageal reflux. The electroencephalogram showed no abnormality, but the electroretinogram and visual evoked response indicated some loss of function of the visual pathways and the brainstem auditory evoked response suggested disturbance of the brainstem pathways. Biochemical examination of serum showed a low albumin concentration and raised transaminase activities, although these abnormalities were less severe than those of his brother (table 1). There was no abnormality involving reducing substances, organic acids, or amino acids in the urine. Plasma amino acid concentrations were normal except those of proline and threonine, which were raised. The concentration of urate was also within the reference range. Thyroid studies showed that the concentration of thyroid stimulating hormone was high (10·8 mU/l; reference range 0·5–6 mU/l), and total thyroxine concentration was low (38 nmol/l; reference range 90–195 nmol/l) as was that of thyroxine binding globulin (3·6 mg/l; reference range 7–17 mg/l). Serum lipid and lipoprotein concentrations were also measured (table 2). The lipoproteins were within the reference range with the exception of apolipoprotein B, the presence of which was indicated by immunoelectrophoresis, though it was not quantifiable.

After confirmation that he had the same condition as his brother his parents wanted him to return home, and he died of pneumonia at the age of 17 weeks. At necropsy, there was bilateral bronchopneumonia, a moderate pericardial effusion, and a small amount of ascites. The liver and brain abnormalities were similar to those of his brother, but the kidneys looked normal.

SUBJECTS

Serum samples from the two patients with olivopontocerebellar atrophy of neonatal onset were analysed together with samples from four groups of control subjects: 300 normal adults, 10 infants and children suspected of having olivopontocerebellar atrophy or DDD syndrome but in whom further investigation confirmed different diagnoses, two children with olivopontocerebellar atrophy of childhood onset with retinal degeneration (type III),[5] and 17 infants aged 6 weeks to 12 months with cirrhosis but without the other features of the neonatal olivopontocerebellar atrophy syndrome (including infants with severely deranged liver function). Samples of serum were stored at −20°C until analysis. Normal cerebrospinal fluid, which contains transferrin with 0–6 sialic acid residues, was used as a reference sample to show the positions of all the transferrin bands (fig 4, lane A).

METHODS

The different forms of transferrin were separated by agarose isoelectric focusing.[13] Briefly, an agarose gel 220×110×1 mm containing 4% carrier ampholytes (Pharmalyte 4–6·5) was loaded with approximately 40 ng of transferrin (2 μl serum diluted 1:100). Focusing was carried out at 1000 V for 30 minutes. After transfer to cellulose nitrate the transferrin was detected immunochemically with sheep antihuman transferrin IgG peroxidase conjugate.

Results

Isoelectric focusing of serum transferrin from normal control subjects showed that transferrin containing four sialic acid residues (tetrasialotransferrin) was the main component (fig 4, lanes B and C). In both of our patients with olivopontocerebellar atrophy of neonatal onset, transferrin isoelectric focusing showed pronounced increases in disialotransferrin and asialotransferrin, with a corresponding reduction in tetrasialotransferrin (fig 4, lanes D and E). In no other sample (including those from infants with cirrhosis caused by disorders other than olivopontocerebellar atrophy, and those from the two children with type III disease) was there a similar alteration of the transferrin isoelectric focusing pattern.

Table 2 Serum lipid and lipoprotein concentrations in case No 2

Analyte (units)	*Serum concentration*	
	Case No 2	*Reference range*
Cholesterol (mmol/l)	3·4	2·3–4·9[19]
Triglycerides (mmol/l)	1·3	0·6–1·9[19]
High density lipoprotein cholesterol (mmol/l)	1·12	0·6–2·2[19]
Low density lipoprotein cholesterol (mmol/l) by Friedewald equation[20]	0·67	1·7–3·4[1]
Apolipoprotein A I (g/l)	1·17	1·15 (0·46)[21]*
Apolipoprotein B (g/l)	<0·30	0·87 (0·58)[21]*

*Mean (2 SD).

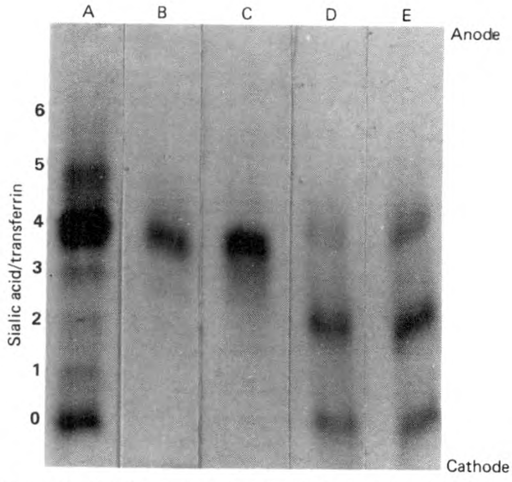

Figure 4 Isoelectric focusing of transferrin from samples of serum and cerebrospinal fluid. (A) Represents normal cerebrospinal fluid, (B) and (C) serum from two normal subjects, and (D) and (E) serum from the two cases of olivopontocerebellar atrophy of neonatal onset. Numbers at the side incidate the bands corresponding to transferrin possessing 0 to 6 molecules of sialic acid.

Discussion

The clinical and pathological findings in our two cases are essentially the same as those described in the four children previously reported with neonatal olivopontocerebellar atrophy.[1 2] All six cases failed to thrive, and had developmental delay, hypotonia, abnormal eye movements, varying degrees of cirrhosis and fatty liver, and typical neuropathogical features. All six cases died before the age of 2 years. This contrasted with the cases of DDD syndrome which, at the time that they were reported, were all alive between the ages of 3 and 21 years.[6] Except for this one aspect, however, the similarities between the two conditions are striking. Features common to both disorders include failure to thrive, hypotonia, developmental delay, retinal abnormalities, joint restrictions, liver disease, pericardial effusion, diarrhoea, and cerebellar atrophy.

Kristiansson *et al* have shown that children with the DDD syndrome have a characteristic alteration in the pattern produced by isoelectric focusing of transferrin from serum and cerebrospinal fluid.[6] Similar biochemical findings were also reported by Jaeken *et al.*[7 10 14] We have now shown that this pattern is also present in cases of olivopontocerebellar atrophy of neonatal onset. Whether this abnormality in the sialic acid content of serum serum transferrin is found in any other condition has been studied intensively. The results of transferrin isoelectric focusing on many thousands of serum samples have shown that similar patterns are seen only in cases of severe alcohol abuse, and these changes are usually less pronounced.[6 15] Our results show that infantile liver disease alone does not cause similar alterations in serum transferrin patterns.

Transferrin is not the only glycoprotein that is abnormal in olivopontocerebellar atrophy of neonatal onset and in the DDD syndrome. For example, low plasma concentrations of thyroid binding globulin and caeruloplasmin have been reported in both conditions.[1 2 8 9] A low serum concentration of the glycoprotein apolipoprotein B has been reported in olivopontocerebellar atrophy of neonatal onset (our case 2 and case 1 reported by Agamanolis *et al*[1]). The results of lipid and lipoprotein analyses in our case 2 failed to show all the abnormalities reported by Agamanolis *et al*; the more generalised lipid abnormalities in the latter case may perhaps be explained by poor nutrition and more advanced liver disease. Interestingly, low concentrations of β-lipoproteins have been found during infancy in some patients with the DDD syndrome.[6]

The biochemical similarities combined with the remarkable clinical similarities between the DDD syndrome and olivopontocerebellar atrophy of neonatal onset suggest that they may represent parts of the range of a single genetic metabolic disease, or at least closely related inborn errors of glycoprotein metabolism. Any hypothesis about the precise site of the metabolic defect must explain how the sialic acid content of serum transferrin becomes deranged, how the serum concentrations of some (but not all) glycoproteins are substantially reduced, and how damage to the liver and parts of the central nervous system occurs. The sialic acid content of serum transferrin could be altered by an inborn error affecting the synthesis of the glycoprotein or by one affecting its degradation.

During synthesis of mammalian glycoproteins, the addition of sialic acid to galactose residues at the non-reducing terminals of antennas of complex asparagine-linked glycans occurs at a late stage in post-translational processing, and results in termination of the chain. It is catalysed by two β-galactoside α-2-3 and α-2-6 sialyl transferases, which show specificity towards both the glycosidic linkage of the receptor galactose residue and the branch on which it occurs.[16] The number and the structure of the recipient oligosaccharide chains are themselves determined by the primary structure of the protein and by the activities of the processing glycosidases and glycosyl transferases in the cell in which it is synthesised. Thus a change in the number of sialic acid residues on the transferrin molecule could, in theory, be the result of a mutation in its structural gene or a change in the activity of any one of the processing enzymes up to and including the sialyl transferases that add the terminal sialic acid residues. A specific mutation in the transferrin gene, however, seems unlikely in view of the changes in other glycoproteins in these patients. The reported decrease in non-specific N-acetylglucosaminyl transferase activity[9] raises the possibility that one of the seven N-acetylglucosaminyl transferases required to generate the range of branched structures in complex glycans may be defective.[17]

Serum sialidases (neuraminidases) can remove sialic acid residues from serum transferrin; the transferrin can then be removed from the circulation by the hepatic asialoglycoprotein receptor.[18] Thus an alteration in the sialylation of serum transferrin could, in theory, result from increased serum sialidase activity or from a defective asialoglycoprotein receptor. The latter mechanism would, however, be expected to lead to an increase rather than a decrease in serum glycoprotein concentrations.

The correct explanation for the defect in the DDD syndrome and olivopontocerebellar atrophy of neonatal onset will probably have to await elucidation of the structure of the normal and abnormal transferrin glycans. The pathogenesis of organ damage is also unknown at present. The effects of a general disorder of glycoprotein metabolism are likely to be complex in view of the pleiotropic role of glycoproteins in cellular processes, cell-cell recognition, and transport.

We thank Dr R M Boustany for supplying serum from patients with olivopontocerebellar atrophy type III, and the technicians at the Medical Research Council Lipoprotein Unit, Hammersmith Hospital, London, for measuring serum lipid and lipoprotein concentrations.

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A spoonful of sugar

Mary Poppins' advice may well upset dentists but there appears to be more to the calming effects of sugar than meets the eye. Workers in Baltimore (Elliott Bass and Lisa Hoffmeyer, *Pediatrics* 1991; 87: 215–8) have shown that giving a small amount of sucrose by mouth to newborn babies before heel prick blood letting reduced the amount and duration of subsequent crying compared with that in babies given only water. Crying in babies after circumcision was also reduced by sucrose. Babies given nothing cried for 67% of the time after the procedure, those given a dummy moistened with water cried for 49% of the time, and those given a dummy soaked in 24% sucrose solution cried for 31% of the time. The effect is thought to outlast the taste of sugar. Previous studies on rats have given similar results and the effect was eliminated by pretreating the animals with an opiate antagonist suggesting that it might be mediated by endogenous opioids.

These studies are of great theoretical interest and sucrose as a calmer for minor procedures seems acceptable but for more painful procedures, including circumcision, it is difficult to justify withholding more effective pain relief. There is no doubt that newborn infants respond to pain and surgical stress[1] and they deserve to be treated properly in this respect.

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Archives of Disease in Childhood 1991; **66:** 1033–1036

Normal postnatal androgen production and action in isolated micropenis and isolated hypospadias

B A J Evans, D M Williams, I A Hughes

Abstract

To try and find out if a defect in androgen biosynthesis or action could be responsible for the incomplete virilisation seen in boys with isolated hypospadias and isolated micropenis, androgen receptor binding was studied in genital skin fibroblasts established from 18 boys with isolated micropenis and 19 boys with isolated hypospadias. The production of gonadotrophins and testosterone was also measured in the boys with micropenis. There was no evidence of gonadotrophin deficiency, or of a defect in testosterone biosynthesis in the boys with micropenis, and there was no evidence of a quantitative or qualitative defect of androgen binding in either group. These isolated abnormalities may be the result of transient defects in androgen synthesis or action, or both, during a critical phase of embryogenesis.

Sexual differentiation in boys follows an orderly sequence of events once the indifferent gonad has developed into a testis. This occurs early in gestation and is under the influence of a testis determining factor, the gene for which is on the short arm of the Y chromosome.[1 2] Adequate testosterone biosynthesis, the onset of which is probably initially spontaneous[3] and which is later controlled by placental human chorionic gonadotropin and pituitary luteinising hormone, is required to induce Wolffian duct development. Male differentiation of the external genitalia is dependent on 5-α-dihydrotestosterone,[4] the active reduced metabolite of testosterone, and both androgens promote phallic growth during the remainder of gestation. The ultimate biological expression of androgen action in target tissues requires the presence of a specific intracellular binding protein that can mediate the effects of androgens on gene expression.[5]

Defects in fetal pituitary secretion of luteinising hormone, testosterone biosynthesis, or androgen action may show themselves as inadequate virilisation of varying severity and sometimes as genital ambiguity. Isolated micropenis and hypospadias are both disorders of inadequate virilisation that are not associated with ambiguity of the genitalia. The former may be the result of congenital hypopituitarism, it may be associated with several dysmorphic syndromes, or it may have no demonstrable cause. Hypospadias is a common isolated malformation with an incidence of 0·2 –0·6%.[6] The defect is the result of failure of complete fusion of the urethral folds, a process mediated mainly by dihydrotestosterone. A defect in androgen biosynthesis or action may be responsible for both these conditions.

We report a study of androgen receptor binding in genital skin fibroblasts established from two groups of boys with isolated micropenis and isolated hypospadias. We also assessed the production of gonadotrophins and testosterone in the group with isolated micropenis.

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Patients and methods

MICROPENIS

Eighteen boys with isolated micropenis were studied. Their ages at the time of study ranged from 4·1 to 16·4 years, and eight were prepubertal with bone ages of less than 10 years. The remaining 10 were pubertal, their Tanner stages ranging from 2 to 4. The stretched penile length was measured by the method of Schonfeld and Beebe and in each case was 2·5 SD or more below the mean value for age.[7] All the boys had normal growth velocity and none was obese.

Serum samples were collected before and 30, 60, 90, and 120 minutes after an intravenous bolus dose of 100 µg luteinising hormone releasing hormone for measurement of luteinising hormone and follicle stimulating hormone. Each boy then received human chorionic gonadotrophin 2000 units daily intramuscularly for three days. A blood sample was collected on the fourth day for measurement of plasma testosterone concentration. A 2 mm scrotal skin punch biopsy was taken under local anaesthetic to establish genital skin fibroblasts in culture for studies of androgen receptors. Informed parental consent (and where appropriate that of the child) was obtained in each case.

HYPOSPADIAS

Nineteen boys with isolated hypospadias were studied when they were admitted to hospital for repair. The defects were all classified as glandular or penile. There were no other anomalies of the penis or associated genital abnormalities. A 2 mm foreskin biopsy was obtained at the time of surgery to establish genital skin fibroblasts in culture.

METHODS

Serum luteinising hormone and follicle stimulating hormone, and plasma testosterone concentrations were measured by radioimmunoassay.[8 9] Bone ages were calculated by the method of Tanner and Whitehouse.[10] Primary explants of skin were established in culture and genital skin fibroblasts were serially subcultured until enough cells were obtained for androgen receptor binding studies. Total receptor concentration, receptor binding affinity, and the effects of increased incubation temperature and prolonged androgen preincubation of cells on specific androgen receptor binding were all measured as previously described.[11,12]

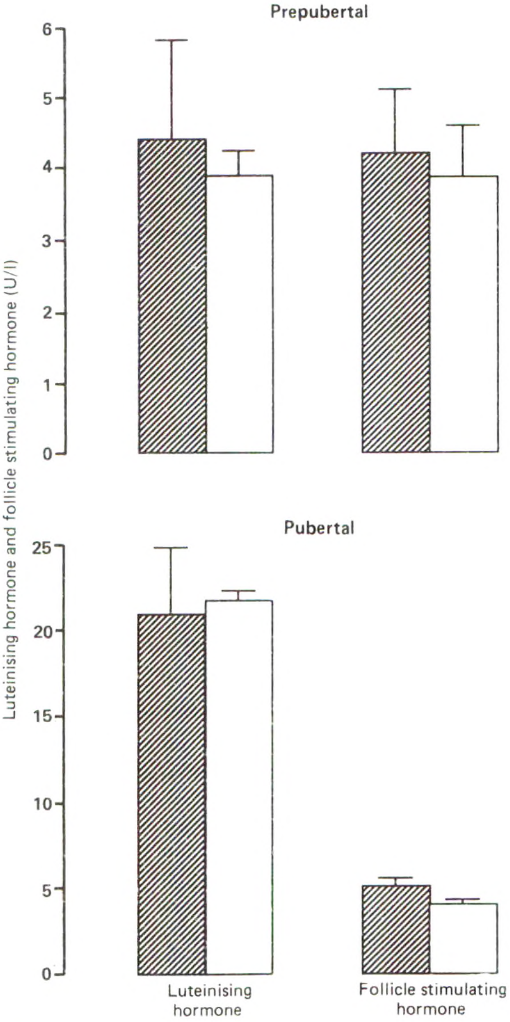

Figure 1 Mean (SEM) peak luteinising hormone and follicle stimulating hormone responses to acute stimulation with luteinising hormone releasing hormone in 18 boys with isolated micropenis. The open bars indicate the response in normal boys (adapted from Hughes[13]).

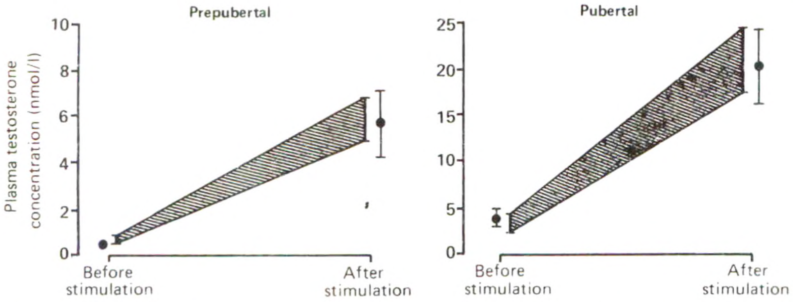

Figure 2 Mean (SEM) plasma testosterone response to stimulation with human chorionic gonadotrophin in 18 boys with isolated micropenis. The shaded area represents mean (SEM) values from normal boys (adapted from Winter et al.[14])

Results

The mean (SEM) peak luteinising hormone and follicle stimulating hormone responses to acute stimulation with luteinising hormone releasing hormone in isolated micropenis are shown in fig 1. There were no significant differences in responses between normal boys ($n=22$) and either pubertal or prepubertal boys with micropenis. The testosterone response to short term stimulation with human chorionic gonadotrophin was measured in the same group of boys (fig 2). The mean (SEM) peak plasma testosterone concentration in prepubertal and pubertal boys was 5·7 (1·4) and 20·3 (4·0) nmol/l, respectively; this response was within the reference range for normal boys of comparable pubertal stage.[14] Figure 3 and table 1 show the results of analysis of androgen receptor binding in genital skin fibroblasts. The concentration of androgen receptors and their binding affinity in both groups of boys were similar to those in normal boys. A number of boys in both groups had apparent increases in receptor concentration compared with normal controls, but there was no evidence of receptor deficiency. There was no evidence of a thermolabile receptor in any cell strain when specific receptor binding was measured after increasing the incubation temperature from 37°C to 40°C.

Prolonged (20 hours) incubation of genital skin fibroblasts with androgen causes an increase (augmentation) in specific receptor binding in normal cell strains.[12] A response is defined as an augmented: basal ratio of binding of 1·4:1 or more (fig 4). The median response was 1·7 in the group with hypospadias and 2·05 in those with micropenis (normal median, 2·1; 10th and 90th centiles, 1·5 and 2·0, respectively). There was a borderline response (a ratio of 1·3:1) in a cell strain established from one boy with hypospadias.

Discussion

Previous studies have suggested that abnormalities of androgen production or action may be possible causative factors in patients with isolated forms of inadequate virilisation such as hypospadias.[15–17] Micropenis has been described in association with pituitary insufficiency or dysmorphic syndromes, but we found no evidence of gonadotrophin deficiency in this group of boys with micropenis who were otherwise normal. Furthermore, there was no evidence of any defect in testosterone biosynthesis based on the plasma testosterone response to stimulation with human chorionic gonadotrophin.

We tried to define some defect in androgen action to explain the incomplete virilisation in boys with isolated micropenis and isolated hypospadias. Genital skin fibroblasts are a useful target tissue to study androgen action in vitro,[18] but we found no evidence of a quantitative defect in either group of boys. The presence of a normal binding affinity for the receptor and the lack of thermolability of the androgen receptor complex excluded a qualitative defect in androgen binding. A recent study that examined only prepubertal boys with hypospadias also

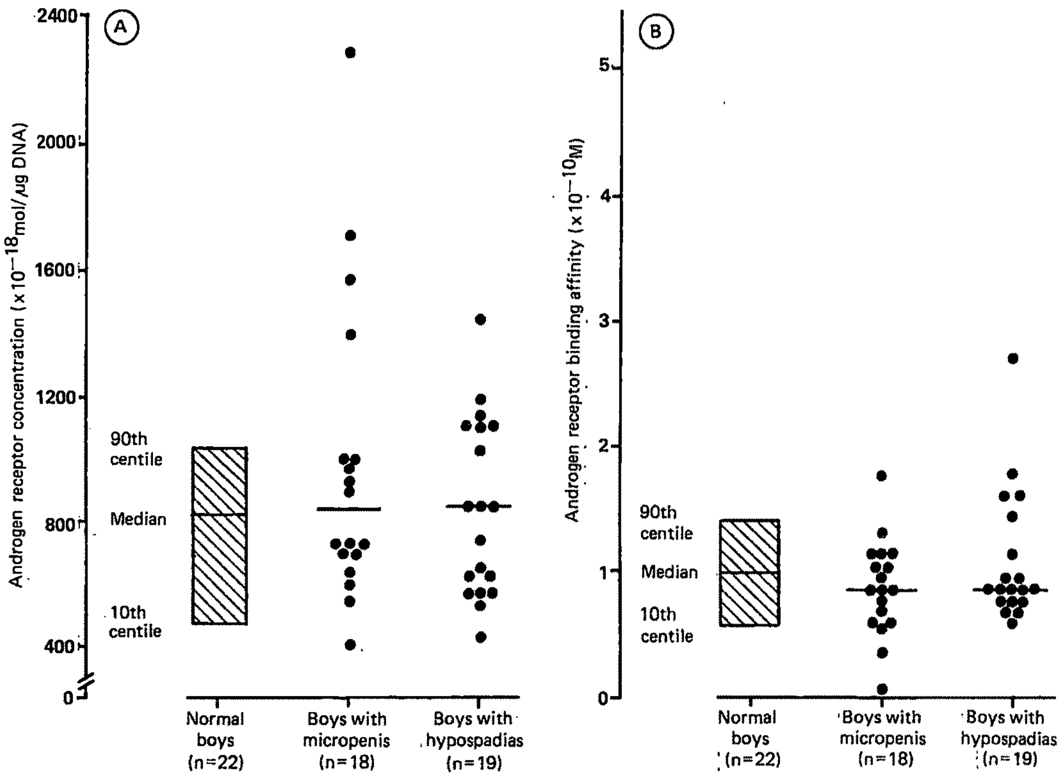

Figure 3 Androgen receptor concentrations (A) and binding affinities (B) in genital skin fibroblasts from 22 normal boys (median, 10th, and 90th centiles), 18 boys with isolated micropenis, and 19 with isolated hypospadias.

Androgen receptor concentration and binding affinity in boys with isolated micropenis and isolated hypospadias compared with normal boys. Normal values are expressed as median (10th and 90th centiles)

	Androgen receptor concentration ($\times 10^{-18}$ mol/μg DNA)	*Androgen binding affinity ($\times 10^{-10}$M)*
Boys with isolated micropenis (n=18)	816	0·86
Boys with isolated hypospadias (n=19)	834	0·83
Normal boys (n=22)	813 (471 and 1034)	0·99 (0·56 and 1·42)

showed an apparently normal androgen receptor.[19] This is in contrast to patients with a partial form of the androgen insensitivity syndrome that is characterised by a number of genital abnormalities including micropenis with chordee, perineoscrotal hypospadias, a bifid scrotum, and undescended testes. Both quantitative and qualitative defects of the androgen receptor have been described in these patients.[11] [12] A recent survey of 70 patients with this syndrome reported a defect in androgen production or action in more than 20% of cases.[20]

We have reported the use of androgen induced augmentation of specific receptor binding in genital skin fibroblasts from patients with micropenis and hypospadias as an in vitro marker of androgen action. The response was normal in each case. The results may provide a useful biological marker of the androgen response in vivo in those patients who require a course of androgens to facilitate repair of hypospadias by prior growth of the penis.

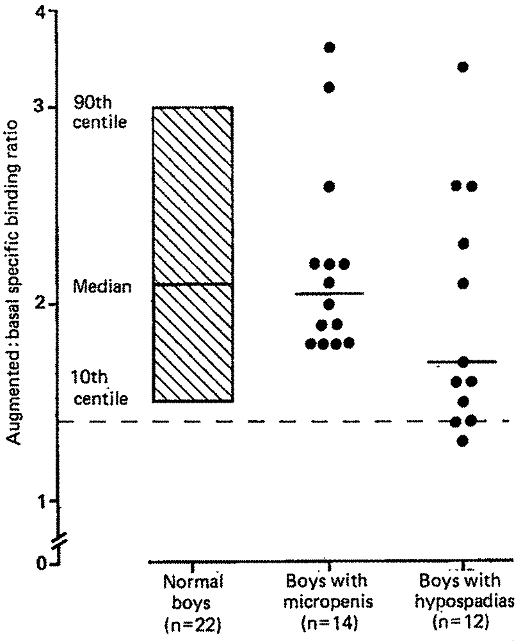

Figure 4 Effect of preincubation of androgen on augmented specific binding activity in 22 normal boys, 14 boys with isolated micropenis, and 12 with isolated hypospadias. A response was defined as an augmented basal ratio of ≥1·4:1 (indicated by the broken line).

The cause of the defect in isolated micropenis and isolated simple hypospadias remains unknown. The more severe and familial forms of hypospadias possibly represent one end of a range of phenotypic expression of the androgen insensitivity syndrome. Now that the gene for the androgen receptor has been cloned,[21] it is possible that molecular genetic analysis may show some defect in this subgroup of patients. It is likely, however, that most of these boys have an isolated genital abnormality that has resulted from some subtle defect, perhaps in the timing of adequate androgen production or action during fetal life.

This work was supported by grants from The Medical Research Council, the Wellcome Trust, and Action Research for the Crippled Child. Mr J Lari, consultant paediatric surgeon, kindly provided foreskin biopsy samples from the patients with hypospadias.

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More evidence on sleeping position and SIDS

Doctors and nurses instinctively avoid the supine position in anaesthetised or otherwise neurologically incompetent patients. Babies are neurologically incompetent compared with adults and health workers might therefore have an aversion to placing them supine. Despite that the evidence that SIDS is more common in babies who habitually sleep prone has steadily accumulated.[1]

A team in Tasmania (Terence Dwyer and colleagues, *Lancet* 1991;**337**:1244–7) has performed both a prospective cohort study and a retrospective case-control study. In the prospective study information about the baby's usual sleeping position was obtained at a home visit at the age of 1 month. Of 15 babies who were later SIDS victims nine (60%) usually slept prone at one month whereas 837 of 2592 (32%) other babies did so. The relative risk for usual prone sleeping position and SIDS was 3·12 (95% confidence interval 1·18 to 8·29). Using multivariate analysis to compare the 15 SIDS victims and 116 controls matched for maternal age, birth weight, availability for interview, and month of birth the odds ratio was 4·47 (1·30–15·43).

In the retrospective case-control study two matched controls were chosen for each SIDS victim. Sixty seven per cent of SIDS cases and 37% of controls had been nursed prone giving an odds ratio of 3·45 (1·59–7·49).

The authors call for a prospective randomised trial, I think unrealistically. I can't see parents being willing to enter such a trial in view of the evidence already avaliable. I know which group I'd put my baby into. It seems to me that the evidence is strong enough for action.

ARCHIVIST

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Archives of Disease in Childhood 1991; **66:** 1037–1042

A dose ranging study of ibuprofen suspension as an antipyretic

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Abstract

A double blind trial was conducted to determine the dose of ibuprofen suspension, which is effective in reducing the body temperature. The principal measure of efficacy was a reduction in axillary temperature of 1°C or more three hours after dosing. A second objective of the trial was to compare the incidence and severity of side effects and the palatability of a range of ibuprofen doses.

Ninety three children were included in the analysis. All four doses of ibuprofen studied (0·625 mg/kg–5mg/kg) were associated with temperature reduction and only the lowest dose failed to satisfy the principal measure of efficacy. The influence of dose on the magnitude of the body temperature reduction was significant and the 5 mg/kg dose achieved the largest mean reduction in body temperature (2°C). The tolerability and palatability of all doses studied were excellent. These findings suggest that ibuprofen is a good alternative to paracetamol as an antipyretic.

Fever is one of the commonest features of illness in children, leads to many hospital admissions, and engenders a great deal of parental anxiety. It remains controversial whether fever causes or is simply associated with febrile convulsions,[1] but much time and effort are spent in reducing the temperature of these children and there is reluctance to discharge such children until they are apyrexial.

With the recognition that aspirin in febrile children is associated with an increased incidence of Reye's syndrome,[2] paracetamol became the only antipyretic agent used routinely in children. If a more potent antipyretic, which was as safe or safer than paracetamol, was available then this would be a valuable addition to the paediatric formulary. If such a drug also had powerful anti-inflammatory and analgesic actions, other symptoms often associated with fever would also be alleviated.

Ibuprofen is a propionic acid derivative that has been used to relieve inflammation and pain for over 20 years and has been available for the treatment of juvenile rheumatoid arthritis since 1979. Although it has also been known for some time that ibuprofen has powerful antipyretic effects in both animal models[3 4] and children,[5] this non-steroidal anti-inflammatory drug has not had a UK product licence for this purpose in children until 1990.

There have been a number of trials that have compared the antipyretic properties of ibuprofen with paracetamol in children[5–8] and this was not the purpose of this present study. It has been established by these trials that ibuprofen compares favourably with paracetamol but the minimum ibuprofen dose that is effective and the comparative tolerance over a range of doses have not been established. We present the results of a double blind trial, the main aim of which was to determine the minimum dose of oral ibuprofen suspension that is effective in reducing fever in children. A second objective was to compare the incidence and severity of side effects of a range of doses.

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Patients and methods

The trial was conducted at the University Hospital, Nottingham, and had the approval of the Nottingham Hospitals ethics committee. Written, informed consent was obtained from a parent or guardian.

In recognition of the difficulties in defining the normal body temperature range of children at different times of day and in different thermal environments, the principal index of antipyretic efficacy chosen was a reduction in body temperature of 1°C or more within three hours of the dose rather than an absolute body temperature. This criterion was defined before the study.

Children of either sex were eligible provided that the axillary temperature on admission to the ward was 37·5°C or more. A body weight less than 8 kg precluded entry to the trial and no child was studied twice. Children were also ineligible if there were relative contraindications to oral non-steroidal anti-inflammatory drugs (bleeding disorder; hepatic, renal or cardiac disease; peptic ulceration; recurrent severe bronchospasm; receiving immunosuppressant treatment, bronchodilators, digoxin or diuretics; previous adverse reaction to aspirin or non-steroidal anti-inflammatory drugs). Children were not excluded if they had received previous antipyretics, antibiotics, or other concomitant drug treatment. Entry to the trial was immediately after the eligibility assessment except when paracetamol or aspirin had been given in the previous four hours in which case these drugs were discontinued and a washout period of four hours was allowed. There were no children taking non-steroidal anti-inflammatory drugs at the time of entry to the trial.

Randomisation to treatment was arranged so that equal numbers of patients were allocated to receive one of four strengths of ibuprofen suspension: 2·5 mg/ml, 5 mg/ml, 10 mg/ml, or 20 mg/ml. An appropriate volume of suspension of one of these strengths was given, depending on body weight, such that the children were effectively randomly allocated to receive one of four doses of ibuprofen suspension: 0·625 mg/kg, 1·25 mg/kg, 2·5 mg/kg, or 5·0 mg/kg. The four study medications were identical opaque orange syrups and similar in taste. Medications were administered using a plastic measuring cylinder and 5 ml of water used to rinse any residual volume of medication from the dispenser. The randomised dose to which the child was allocated was repeated six hours after the initial dose.

It was considered unethical to include a placebo control group. To meet the concern that the weaker ibuprofen regimens might prove ineffective a supplementary medication was provided by ibuprofen 2·5 mg/kg (10 mg/ml strength of suspension). In the event that the axillary temperature remained above 37·2°C three hours after the initial randomised dose of ibuprofen, a 'rescue' dose of supplementary medication could be administered. If the child was given this 'rescue' dose, no medication was given at six hours after the initial randomised dose but the child received a second dose of the supplementary medication at nine hours.

The demographic data collected on entry to the trial consisted of age, sex, body weight, and concomitant treatment. The axillary temperatures of the children were recorded using a digital thermometer (Comark Products International) immediately before the initial dose (baseline) and at 0·25, 0·5, 1, 2, 3, 4, 6, 9, and 12 hours after the initial randomised dose of ibuprofen. These measurements were very reproducible (within observer variation ±0·1°C). The clinical condition of the child was evaluated 3, 6, and 12 hours after the initial dose by one 'blind' investigator (SCM) on a five point scale with categories much worse, worse, no change, improved, and much improved. The acceptability of the medication to the child was assessed by the same investigator on a five point scale (very acceptable, acceptable, indifferent, unacceptable, very unacceptable) at the initial and repeat dosings.

All adverse clinical events that occurred during the 12 hour period of the trial were recorded irrespective of whether or not these events were considered to be a side effect of ibuprofen. The case notes of children for whom an adverse event was recorded were subsequently reviewed by one of us (DH), who remained 'blind' to which dose of ibuprofen the children had been randomised and who made an assessment of whether the adverse event was part of the natural history of the child's condition or a side effect of ibuprofen.

STATISTICAL ANALYSIS

The effect of different doses on the number of patients withdrawing were compared using the χ^2 test. The change in temperature at three hours from baseline was analysed for each dose of ibuprofen using the paired *t* test and 95% confidence intervals were calculated for the mean differences between baseline axillary temperature and the temperature at three hours. Differences between doses in the temperature at three hours, the clinical condition at three hours, and the acceptability of the medication were tested by analysis of covariance, using age and baseline temperature as the covariates. Differences between doses in the number of children who warranted supplementary medication were compared using the χ^2 test. The effects of different doses on the number of children suffering adverse clinical events were compared using the χ^2 test.

Results

One hundred children were recruited into the study. Seven of the children who had been entered did not, in retrospect, fulfil the eligibility criteria. The 93 remaining children (57 boys and 36 girls) were included in the analysis. Their mean (SD) age was 2·6 (1·7) years, mean body weight 13·1 (4·2) kg, and mean baseline axillary temperature 38·6 (0·7)°C. Twenty two (24%) of these children were already receiving some medication when recruited to the study. The four treatment groups showed no significant differences in age, weight, baseline, axillary temperature, or frequency of concomitant treatment (table 1).

WITHDRAWALS FROM THE TRIAL

Of the 93 eligible children who received a first randomised dose of ibuprofen, 18 children were withdrawn from the trial by the clinical investigator before the 12 hour study period was completed. The reasons were lack of response, as judged by an axillary temperature persisting above 37·2°C despite a 'supplementary' dose of ibuprofen at three hours (n=13) or an adverse event (n=5). In addition, one child made a complete recovery and was discharged from hospital before completion of the 12 hour period, and there were incomplete data for a further four children. In total, therefore, the data set analysed was incomplete for 23 of the 93 children deemed eligible to enter the study. There was no significant preponderance of these 23 children among the four treatment groups (table 2).

Table 1 Demographic data of children eligibly entered into the trial

	Ibuprofen dose (mg/kg)				
	0·625	*1·25*	*2·5*	*5·0*	*All*
Mean (SD) age (years)	2·4 (1·3)	2·7 (1·8)	2·5 (1·8)	2·8 (2·1)	2·6 (1·7)
Mean (SD) weight (kg)	13·1 (3·6)	12·6 (3·1)	12·7 (3·6)	14·0 (5·9)	13·1 (4·2)
Mean (SD) baseline temperature (°C)	38·5 (0·6)	38·6 (0·6)	38·4 (0·7)	39·0 (0·9)	38·6 (0·7)
No of children entered	26	20	24	23	93
No receiving concomitant treatment	5	7	7	3	22

Table 2 Reasons for withdrawal of patients from study

	Ibuprofen dose (mg/kg)				
	0·625	*1·25*	*2·5*	*5·0*	*All*
Trail status:					
Not withdrawn	19	17	18	16	70
Withdrawn	7	3	6	7	23
Withdrawal category:					
Complete recovery	—	—	1	—	1
Lack of response	3	3	4	3	13
Adverse events	1	—	1	3	5
Incomplete follow up	3	—	—	1	4
Total No of patients in treatment group	26	20	24	23	93

Table 3 Mean (SE) temperature falls by time and treatment group

Time (min)	*Ibuprofen dose (mg/kg)*			
	0·625	*1·25*	*2·5*	*5·0*
15	−0·1 (0·1)	−0·1 (0·1)	−0·2 (0·1)	−0·6 (0·2)
30	−0·3 (0·1)	−0·5 (0·2)	−0·3 (0·1)	−0·7 (0·2)
60	−0·9 (0·1)	−0·8 (0·2)	−0·8 (0·1)	−1·1 (0·2)
120	−1·1 (0·2)	−1·1 (0·2)	−1·1 (0·2)	−1·9 (0·2)
180	−0·7 (0·2)	−1·3 (0·3)	−1·3 (0·2)	−2·0 (0·2)

TEMPERATURE REDUCTION

There was a significant decrease in temperature at three hours for all four doses of ibuprofen ($p<0·01$) with the largest decrease for the highest dose of ibuprofen (table 3). The mean axillary temperatures of the children in the four randomised groups at baseline and three hours after the first ibuprofen dose are shown in fig 1. Interpretation of the data after three hours is confounded by the supplementary doses given to some children resulting in children within one randomised group having received doses which overlap with another group. Analysis of covariance showed that the influence of dose on the magnitude of the body temperature reduction was significant ($p=0·02$), a higher dose of ibuprofen being associated with a lower axillary temperature three hours later. The mean temperature at three hours after the 0·625 mg/kg dose was significantly greater ($p<0·01$) than that for the 5·0 mg/kg dose and this was despite the 5·0 mg/kg group starting with the highest mean baseline temperature (fig 2).

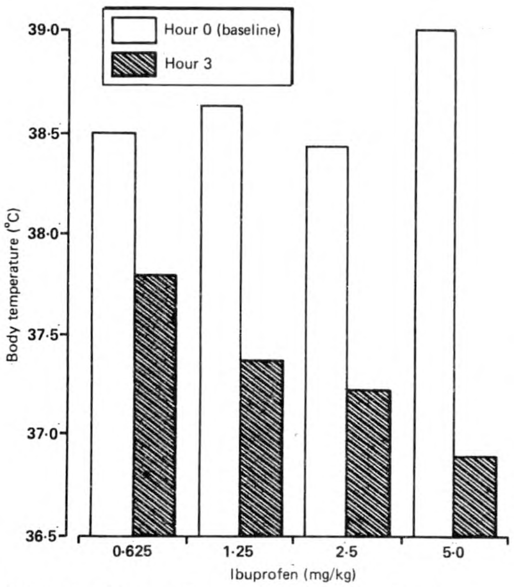

Figure 1 Mean axillary temperature (°C) at hour 0 (baseline) and three hours after ibuprofen.

In order to assess the rate of axillary temperature reduction, mean axillary temperatures at intervals over the first three hours of the study are shown in figure 2. In all but the 0·625 mg/kg ibuprofen group, there was a steady reduction in mean axillary temperature over the first three hours after the initial dose of ibuprofen. The mean axillary temperature of the 0·625 mg/kg group rose from 37·5°C at two hours to 37·8°C at three hours. The reduction in axillary temperature between two and three hours in the other three groups was only 0·1–0·2°C. That is to say, in the three higher dose groups most of the temperature reduction achieved by three hours (fig 1) had already occurred by two hours.

SUPPLEMENTARY DOSE OF IBUPROFEN

A total of 39 out of the 93 children warranted the 'rescue' dose at three hours after the initial, randomised dose and these children were *not* evenly distributed between the four randomisation groups (table 4). The higher the initial dose of ibuprofen, the more likely the children were to have an axillary temperature below 37·2°C at three hours. The proportions receiving a 'rescue' dose at three hours were 68%, 47% 42%, and 23% for the 0·625, 1·25, 2·5, and 5·0 mg/kg ibuprofen groups respectively. These represent significant differences ($p=0·03$).

CLINICAL SCORE

Although there appears to be a trend with lower doses resulting in less clinical improvement, the differences between the scores at three hours did not reach significance (table 5). Interpretation of the data after three hours is confounded by the supplementary medication given to some children.

ACCEPTABILITY OF THE MEDICATION

There were no significant differences in the acceptability of medications containing diffe-

Table 4 Number of children receiving supplementary medication (2·5 mg/kg ibuprofen at three hours if axillary temperature >37·2°C)

	Ibuprofen dose (mg/kg)			
	0·625	*1·25*	*2·5*	*5·0*
No of children given supplementary dose	15	9	10	5

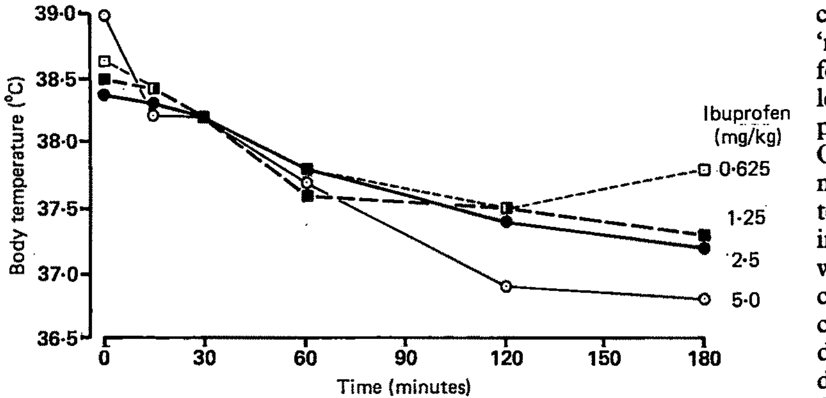

Figure 2 Reduction of axillary temperature (°C) of children taking four different ibuprofen doses.

Table 5 Assessment of clinical condition at three hours by treatment group (a high score is more favourable)

	Ibuprofen dose (mg/kg)			
	0·625	*1·25*	*2·5*	*5·0*
No of children rated at each score:				
1=Much worse	3	1	0	1
2=Worse	4	2	1	0
3=No change	2	4	5	5
4=Improved	7	7	12	4
5=Much improved	3	6	6	11
Mean score	3·2	3·8	4·0	4·1

rent strengths of ibuprofen (table 6). The mean acceptability scores of the medications at first dosing were 2·0, 1·9, 2·0, and 2·2 for the 0·625, 1·25, 2·5, and 5·0 mg/kg ibuprofen groups respectively (1=very acceptable, 2=acceptable, 3=indifferent). Overall, the medication was assessed as acceptable (that is, a score of 1–3) in 93% of the children at the time of the first dose.

ADVERSE EVENTS

A total of 19 adverse clinical events were recorded in 17 children during the study periods (table 7). Five children vomited, seven children had behavioural changes ranging from 'more miserable' to 'delirious', there were five febrile convulsions (all in children admitted following a febrile convulsion), one child developed diarrhoea, and one child manifested a rash. On review of the case notes, only the fine, pink, macular rash was thought to be probably related to the treatment. The other 18 adverse events, including the five adverse events resulting in withdrawal of children from the study, were considered to be due to a worsening of the child's pre-existing febrile illness rather than due to the study medication. The incidence of drug related side effects in this study was therefore 1%. The differences between the numbers of adverse clinical events reported for the four treatment groups were not significant.

Table 6 Acceptability of medication at first dosing (a high score represents less acceptable)

	Ibuprofen dose (mg/kg)			
	0·625	*1·25*	*2·5*	*5·0*
No of children rated at each score:				
1=Very definitely acceptable	9	9	7	6
2=Definitely acceptable	9	5	12	9
3=Indifferent	6	5	4	6
4=Definitely not acceptable	2	1	1	2
5=Very definitely not acceptable	0	0	0	0
Mean score	2·2	1·9	2·0	2·2

Table 7 Summary of adverse events reported

	Ibuprofen dose (mg/kg)			
	0·625	*1·25*	*2·5*	*5·0*
Total No of patients at risk	26	24	26	24
Total No with adverse events:	2	3	6	6
Vomited/nausea	1	—	1	3
Febrile convulsion	1	1	1	2
Delirious	—	1	—	—
Distressed	—	1	—	1
Irritable/agitated	—	—	2	—
Uncomfortable	—	—	1	—
Miserable	—	—	1	—
Rash	—	—	1	—
Diarrhoea	—	—	—	1
Total No of reports	2	3	7	7
Total No drug related	—	—	1	—

Discussion

This dose ranging study was designed as a prospective, mutiple dose, parallel group, double blind trial in which children received 0·625–5·0 mg/kg/dose of ibuprofen. Before this study the standard management of fever in our unit included 10 mg/kg/dose of paracetamol every four hours and it was therefore considered unethical to include a placebo control group in the trial. However, in view of the justifiable concern that children randomised to receive the lower dose ibuprofen regimens might actually receive an ineffective dose, a 'safety net' allowed for supplementary dosing with ibuprofen should the child remain febrile.

This study showed clear dose dependent effects of ibuprofen on the absolute magnitude of temperature reduction, the pattern of temperature change with time, and the need for the child to be given an extra 'rescue' dose of medication. Ibuprofen suspension was equally effective irrespective of age within the range studied.

To determine the minimum effective dose requires criteria to be set that define efficacy. Clearly time has to be included in any definition. An agent that works too slowly will not be clinically useful while a drug that works quickly but then fails to prevent the pyrogen, or the body's physiological response to a falling body temperature, raising body temperature again almost immediately is also unsatisfactory. It was therefore decided to adopt for the study protocol a reduction of 1°C or more in axillary temperature at three hours as the principal measure of antipyretic efficacy. In the 5 mg/kg dose group, 82% of the children achieved a temperature reduction of at least this size (fig 3).

In a study directly comparing a 5 mg/kg/dose of ibuprofen and a 10 mg/kg/dose of paracetamol in febrile children, it was shown that both were superior to placebo and that 5 mg/kg ibuprofen suspension was as well tolerated as 10 mg/kg paracetamol elixir.[8] Two other trials in children have shown that a slightly larger dose of 6 mg/kg ibuprofen as elixir[9] or tablets[6] was as effective in reducing temperature as 10 mg/kg aspirin or 12·5 mg/kg paracetamol respectively. A dose of 5–10 mg/kg ibuprofen is recommended for children with Still's disease.[10] In the study by Walson *et al* 10 mg/kg ibuprofen produced significantly greater and longer last-

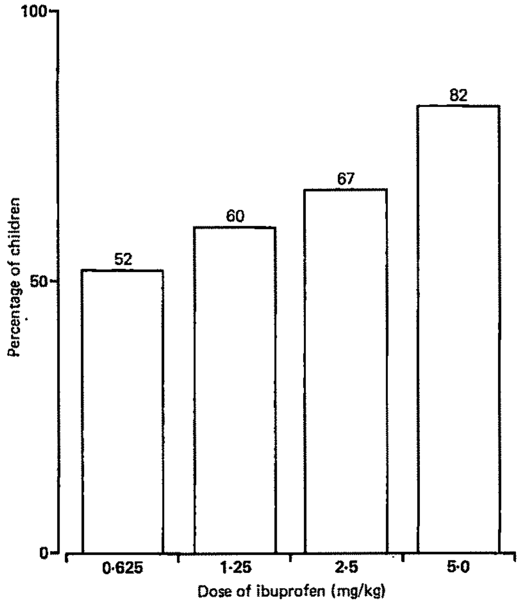

Figure 3 Percentage of children showing a temperature reduction of 1°C or more at three hours by dose of ibuprofen.

ing fever control than 10 mg/kg paracetamol.[8] However, doses of 15 mg/kg paracetamol are commonly prescribed.

Although 39 children warranted 'rescue' treatment, only five of these children had received an initial 5 mg/kg dose of ibuprofen. The 'rescue' medication was given if the child's axillary temperature remained above 37·2°C three hours after the initial randomised dose and the apparent 'failure' of the 5 mg/kg dose in these five children must be viewed against this very strict temperature criterion and in comparison with other antipyretic measures. The mean baseline axillary temperature was 39°C in the 5 mg/kg ibuprofen group of our study. In an earlier study in which children had a mean baseline oral temperature of 39°C, the mean oral temperature three hours later remained at 38·7°C if only nursing measures were used and was 37·8°C if 10 mg/kg paracetamol had been given.[8]

Finally, the 5 mg/kg ibuprofen dose did not compare unfavourably in our study with the weaker doses in acceptability or in the nature of adverse events.

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Commentary

NEW DRUG FOR OLD?

Fever is universal. We all experience it from time to time and the average child in Britain is given an antipyretic drug on four or five days a year.[1] Since the demise of aspirin for childhood fever in 1986, paracetamol has had the field to itself. Fever in itself is unlikely to be harmful. As a response to infection it almost never rises above 41°C and, provided dehydration is avoided and heat loss is not prevented by overheating or overclothing, fever of that degree is not damaging.[2] Even in those prone to febrile convulsions, treatment of fever does not seem to prevent attacks.[3] The reasons for giving an antipyretic drug are to relieve discomfort and to relieve the anxiety felt particularly by parents (and by medical and nursing attendants). Do we need a new drug for this purpose and what risk are we prepared to take to develop one?

Paracetamol was first used in 1893 and has been in regular use since 1949.[4] It has so far not been associated with serious toxicity in therapeutic dosage and, despite its ready availability, overdosage has not been a serious problem in children.[5] It is effective.[6–8]

What properties should a drug have in order for it to replace paracetamol as an antipyretic for children? Laying aside considerations of presentation and expense, I suggest the following: (i) it should be demonstrably more effective *in relieving discomfort* and (ii) it should be free of serious toxicity when given to *very large numbers* (millions) of children. Therein lies the rub. Does a possibly slightly greater temperature reduction with ibuprofen translate into significantly greater comfort for children in practice? There seems to be little evidence on that point. The second of these conditions is, of course, impossible to satisfy without taking the risk and whether the risk is worthwhile depends on the seriousness of the condition to be treated and the effectiveness of present treatment. If aspirin were a certain cure for leukaemia, for instance, its association with Reye's syndrome would be disregarded in that context because the benefit would far exceed the risk. The risk-benefit equation is very different for childhood fever.

So far there is no known serious toxicity for ibuprofen but it has not until very recently been used in very large numbers of children. It has been used in the treatment of juvenile chronic arthritis for 11 years but only recently been used as an antipyretic.[9] Aspirin was in use for over 80 years before its use in children was discontinued. Drug surveillance is now much improved but to recommend any drug for use in a condition that affects virtually all children several times a year is to suggest an experiment. There are many other non-steroidal anti-inflammatory drugs, the manufacturers of at least one of which have to my knowledge seriously considered promoting its use for childhood fever but have so far not done so, so the number of experiments can be expected to proliferate. Such experiments should be driven by need. Do we need them?

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Reply to the commentary by the authors

We are not proponents of any particular drug for children. We are, however, proponents of choice in prescribing for children and this choice should be well informed. The purpose of our study was to determine the minimum effective dose of ibuprofen for childhood fever, and the safety of this drug in this context, rather than to compare it directly with paracetamol, which others have done. Whether ibuprofen should have been granted a product licence as a childhood antipyretic is a decision for the Medicines Control Agency, which enforces the Medicines Act 1968.

The commentary states that paracetamol overdosage has not been a serious problem in children. However, in the reference quoted it is stated that 'since the withdrawal of paediatric aspirin formulations, the incidence of accidental paracetamol poisoning in children appears to be increasing'.[1] Although hepatotoxicity and death are rare in children under the age of 5 years,[2] this is probably because children ingest smaller doses and present earlier for treatment than adults. If an entire bottle of paediatric ibuprofen suspension were ingested by a child aged 1 to 2 years, serious toxicity would be unlikely.[1]

The consideration that an antipyretic drug should relieve discomfort is an important one. Analgesia for children has perhaps not always been given the attention that it deserves. Ibuprofen has been used as an analgesic and anti-inflammatory drug in childhood arthritis for some time[3] and at much larger doses than in our study. Although fever may be seen by doctors as a trivial and common feature of childhood illness, the discomfort which accompanies febrile illnesses is very real to that child. It has been estimated that over 240 million doses of ibuprofen have been given to children. To try to improve the relief of pain is not to experiment, provided we adhere to the principle of *primum non nocere*. It is surely better that drugs used for children are subjected to the same scrutiny as those introduced for adults, rather than these drugs being absorbed into the paediatric formulary on an *ad hoc* basis, as has been the case with many other childhood treatments over the last decades. Perhaps if aspirin had been subjected to the same scrutiny, and the same surveillance after it was marketed,[4] the association with Reye's syndrome would have been detected before 80 years had elapsed?

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Evaluation of paediatric intensive care in a regional centre

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Abstract

All 162 consecutive admissions to a multidisciplinary paediatric intensive care unit in the UK have been prospectively evaluated in terms of therapeutic intention, sickness levels, age, utilisation of resources, and outcome. For 101 (62·3%) of the children admitted the aim of treatment was to cure the condition but for 30 (18·5%) ultimately only a palliative option was available. Five children were admitted to avail of specialised monitoring facilities. One half of the children admitted were physiologically unstable. The majority (102, 62·9%) were age 12 months or less. Resource utilisation, which was not affected by therapeutic intention, was greatest for the sickest patients, those age 1 month or less and non-survivors. Mortality rate overall was 17·9%. Mortality was unaffected by age and therapeutic intention and was inversely related to level of sickness.

The information provided by this study forms a basis for medical audit within the unit and is essential for meaningful comparisons of standards of care and outcome with other units.

Paediatric intensive care has developed as a unique specialty in the past 20 years. Guidelines exist for the facilities, organisation, staffing, and training required for this service.[1–3] Although the provision of paediatric intensive care is expensive, accounting for 20% of the hospital bill,[2] detailed evaluation has not been undertaken in the UK and there is also only limited European data available.[4 5] Deficiency of this information will inhibit further development of paediatric intensive care.

Consequently this study has been undertaken to document admission criteria, sickness levels, resource utilisation, and outcome of patients admitted to a multidisciplinary, regional paediatric intensive care unit.

Patients and methods

Northern Ireland has a population of 1·6 million people, most of whom live in rural or semirural areas. Belfast is the only sizable city and no part of the province is more than 100 miles from Belfast by road. As there is a good network of roads throughout the province this means that two hours is the maximum time taken to transport any sick child to the paediatric intensive care unit in the Royal Belfast Hospital for Sick Children. This six bedded unit, opened in 1970, provides a comprehensive intensive care service, admitting neonates with surgical problems, neonates with respiratory disease if beds in the special care baby unit are not available, and infants and children with medical and surgical illnesses (table 1).

All consecutive admissions over an eight month period were prospectively studied. On admission patients were classified according to age, Clinical Classification System,[6] and management goals.

The Clinical Classification System provides a method of qualitatively assessing care requirements and correlates well with quantitative measures of sickness.[7–9] Four classes of patients are defined. Class 1 patients are hospitalised patients not requiring intensive care unit facilities. Class 2 patients need the observation capabilities of the intensive care unit and the class 3 group, although physiologically stable, require intensive nursing care. Class 4 patients are physiologically unstable and require frequent medical and nursing interventions.

Four management categories were considered possible for each individual.[10] If the treatment intention was definitive the management was described as 'curative', an example being a child treated for meningococcaemia. If the patient's condition could ultimately be cured but the current treatment was not definitive the goal category was 'palliative option'. If no definitive treatment was foreseeable at any stage the category was 'palliative no option'. For example, each neonate undergoing the first step of staged correction of oesophageal atresia was allocated to the palliative option group and any child with the Arnold-Chiari malformation having a ventricular shunt revised was allocated to the palliative no option group. The fourth group of children, admitted solely for specialised monitoring, was designated as 'monitored'.

The severity of illness was evaluated for all children using the Therapeutic Intervention Scoring System (TISS),[11 12] which was first scored from admission time to 12 noon (admission score) and for each subsequent 24 hour period for the duration of stay. The TISS quantifies 72 therapeutic options available in the paediatric

Table 1 Primary specialty service responsible for admission (n=162)

Specialty	*No (%) of admissions*
Surgery and orthopaedics	61 (37·65)
Medicine	47 (29·0)
Cardiology	13 (8·0)
Cardiovascular surgery (postoperative)	6 (3·7)
Otolaryngology	17 (10·5)
Neurosurgery	15 (9·3)
Neonatology	3 (1·85)

intensive care unit, on a scale of 1 to 4. For example, a score of one point is awarded for the necessity for a single intravenous line or for the provision of chest physiotherapy, and the use of peritoneal dialysis or intracranial pressure monitoring scores four points for each. All treatments other than extracorporeal membrane oxygenation and the use of the intra-aortic balloon pump were available in our unit. One modification was made for young patients by allocating three points for administration of blood products in excess of 20% total blood volume per 24 hour period. The Physiologic Stability Index[9, 12] was scored for class 4 patients simultaneously with the TISS scores. The Physiologic Stability Index is a physiologically based classification designed to assess objectively the severity of illness of paediatric patients. Thirty four variables with limits assigned depending on age and clinical importance are scored 0, 1, 3, or 5. For example, a heart rate of 180 beats per minute is scored one point in an infant or three points in an older child and a urine output of 0·5 ml/kg/hour is scored one point and three points if less than this. The most abnormal value per 24 hours is used for scoring and daily scores derived by summing the individual scores.

Scores for all patients were determined by the same observer (JMcA) for consistency of assessment. The mean TISS scores/patient/day for clinical class, management goal, and age groups were calculated. Admission, mean and maximum TISS and physiologic stability scores were also calculated for class 4 survivors and non-survivors. Survival was defined as surviving to discharge from the unit. Days of intensive care were recorded for each individual and resource utilisation for the described categories estimated from the total days in the intensive care unit and TISS scores/patient/day.[10]

Comparison between group means was by Student's *t* test. As durations of stay were not normally distributed the Mann-Whitney U test was used for comparisons. Mortality numbers were compared by χ^2 analysis, χ^2 with Yates's correction or Fisher's exact test as appropriate.

Results

There were 162 consecutive admissions during the eight month study period with stays ranging from 1–94 days (median 3). A total of 133 (82%) survived to be discharged from the unit and no child died within one month of discharge. Physiologically unstable patients (class 4) comprised 50% (table 2). Mortality was inversely related to clinical class with all class 2 patients surviving. Resource utilisation in terms of days in the intensive care unit and TISS scores were significantly different between the four classes of patients. The mean (SEM) TISS score for the 24 hour period before discharge for survivors was 13·42 (0·66).

GOAL OF TREATMENT

Therapeutic intention was curative for the majority (101, 62·3%) of children and palliative no option for 30 (18·5%). Five children were admitted to avail of the intensive care unit monitoring facilities such as continuous radial artery pressure recording. The mean (SEM) TISS scores, 21·72 (1·17) in the curative group, 18·43 (1·45) in the palliative no option group, and 17·57 (1·6) in the palliative option group, were not significantly different (table 3). There was also no difference between the groups for length of stay or rates of survival.

AGE

The majority of the children (102, 62·9%) were age 12 months or less (neonates and infants); this included 33 neonates. The remaining 60 children were aged up to 15 years.

The neonatal group had primarily surgical problems except for three babies with respiratory distress admitted because no local special care baby unit cots were available. Neonates had the longest stay in the unit and older children the shortest (table 4). TISS scores were also higher for neonates than infants. Consequently resource utilisation was greatest for the neonates and less for older children. Survival rates were not significantly different between the groups.

Table 2 Comparison of clinical classes

	Class 2 (n=28)	*Class 3 (n=53)*	*Class 4 (n=81)*
Median (range) stay (days)*	2 (1–4)	2 (1–12)	6 (1–94)
Mean (SEM) TISS score/patient/day†	7·18 (0·64)	16·62 (0·96)	26·48 (1·09)
95% Confidence interval	5·87 to 8·5	14·73 to 18·5	24·35 to 28·6
% Survival	100·0	92·4	69·1

*p=0·01 between all classes; †p<0·001 between all classes.

Table 3 Comparison of therapeutic goals

	Curative (n=101)	*Palliative no option (n=30)*	*Palliative option (n=26)*	*Monitored (n=5)*
Median (range) stay (days)*	4 (1–58)	2 (1–94)	4·5 (1–41)	2 (1–2)
Mean (SEM) TISS score/patient/day*	21·72 (1·17)	18·43 (1·45)	17·57 (1·6)	3·8 (0·92)
95% Confidence interval	19·4 to 24·0	15·58 to 21·28	14·3 to 20·9	1·26 to 6·34
% Survivors*	81·2	76·7	88·5	100·0

*No significant difference between curative and palliative groups.

Table 4 Comparison of age groups

	Neonates *(n=33)*	*Infants* *(n=69)*	*Others** *(n=60)*
Median (range) stay (days)†	7 (1–58)	3 (1–94)	2 (1–50)
Mean (SEM) TISS score/patient/day‡	23·84 (1·54)	19·37 (1·34)	18·5 (1·45)
95% Confidence interval	20·81 to 26·86	16·74 to 22·0	15·6 to 21·4
% Survivors§	78·8	84·0	81·7

*Aged up to 15 years.
†p=0·01 between neonates and infants and neonates and others; no significant difference between infants and others.
‡p<0·05 between neonates and infants and neonates and others.
§No significant differences between groups.

Table 5 Comparison of class 4 patients for outcome (results are mean (SEM) and 95% confidence interval (CI) except where shown otherwise)

	Survivors *(n=56)*	*Non-survivors* *(n=25)*
Median (range) stay (days)*	7 (2–58)	4 (1–94)
Admission TISS score*	29·9 (1·25)	35·04 (2·66)
95% CI	27·4 to 32·4	29·5 to 40·5
TISS score/patient/day†	23·71 (0·99)	32·19 (2·48)
95% CI	21·8 to 25·6	27·3 to 37·
Maximum TISS score‡	32·9 (1·21)	39·52 (2·47)
95% CI	30·5 to 35·3	34·7 to 44·4
Admission score for physiological stability§	10·39 (0·75)	16·6 (1·76)
95% CI	8·89 to 11·9	13·0 to 20·3
Score for physiological stability/patient/day†	8·41 (0·48)	15·85 (1·7)
95% CI	7·47 to 9·34	12·51 to 19·9
Maximum score for physiological stability†	15·5 (0·77)	19·54 (1·56)
95% CI	13·98 to 17·01	16·48 to 22·59

*No significant difference between survivors and non-survivors; †p<0·001; ‡p<0·01; and §p<0·05.

CLASS 4 PATIENTS

This group constituted half of all admissions. There was no significant difference between length of stay for survivors and non-survivors. There were significant differences between TISS scores and scores of physiological stability (table 5).

Discussion

This study provides the first prospective evaluation of therapeutic goals, severity of illness, and resource utilisation in a multidisciplinary paediatric intensive care unit in the UK. Comparison with the pooled European data highlights similarities and differences.[4] No class 1 patients were admitted to our intensive care unit; however, this group comprised 6% of admissions to eight European units.[4] The percentage admitted for observation (17·3%) was the same as the European experience (17·5%). The proportion of class 4 patients was high in comparison with the European average (39·5%), although two units had 51% and 54% class 4 patients. The Clinical Classification System is a subjective classification but comparison of the mean (SEM) admission treatment scores of physiologically unstable patients in the two studies (31·51 (1·21) in the UK compared with 26·04 (11·3) in Europe) confirms that there was a real difference in admission patterns. This difference may be partly explained by the relatively small size of our unit for the population served. The demand for the beds is consequently usually high. However, it has also been our observation that when space is available there is a tendency for more physiologically stable patients to be admitted. Rothstein and Johnson in their study of an American multidisciplinary unit reported over 60% of admissions scoring less than 10 TISS points and having a mean stay of 1·6 days.[13] They concluded that only patients with care requirements scoring >10 points require admission to an intensive care unit. The mean score for the 24 hours before discharge of live children in our study (13·42) suggests that the unit was used relatively efficiently. However, Pollack *et al* reported higher last day TISS scores than us from a similar American unit.[7] Unfortunately there is no transitional care unit in our hospital to which the children can be discharged and they must be sent directly to the wards. This situation encourages the consultant in the intensive care unit to delay discharge on occasions when the receiving ward has difficulty providing close observation for the child. During the study period no patient required readmission for collapse or died shortly after discharge demonstrating that the strategy is effective. This lack of an intermediate care facility partly explains the longer mean days in paediatric intensive care of sick patients in the UK (10·44) and Europe (9·1) compared with the US (<5,[7] 6·8,[8] 5·5[10]).

Resource utilisation was the same whether a cure was possible or not, reflecting similar levels of sickness between the groups. This also indicates that the responsible consultants had an optimistic approach to treatment and did not discriminate between patients on the basis of possible long term outcome. This approach has important implications for the provision and utilisation of services and resources other than those of the intensive care unit and is itself the subject of a complementary study in the unit addressing the long term consequences of intensive care provision. In terms of short term survival this approach is justified as there was no significant difference in the survival rates between the goal groups.

The majority of the children were 1 year or younger (63%) as was the case in the European centres (72%). This differs from American experience with most of the patients in the USA greater than 12 months old.[7–10] This may reflect a preference not to admit neonates to these units. In our paediatric intensive care unit, neonates with respiratory disease are not usually admitted explaining the much higher proportion in European centres (37·2%). Duration of stay was significantly greater for neonatal patients partly accounting for the shorter mean stay of all patients in American units. We confirmed the finding of Beaufils *et al* that TISS scores were also greater for neonates.[4] Obviously the age mix of the population in the paediatric intensive care unit in addition to the availability of transitional care beds has important implications for the utilisation of available resources. The survival rates were the same for our age groups but mortality was greater for the neonates in the European study. This could be explained if the sickness levels in the European babies was greater than ours but comparison of the mean (SEM) admission TISS scores (27·42 (1·98) in the UK compared with 21·7 (11·87) in Europe) does not support this. However, this possibility cannot be completely ruled out as the maximum scores may have been greater in Europe but are not reported by Beaufils *et al.*[4] It is also possible that the mortality figures reflect the different populations of babies with respiratory disease as there were only three babies (1·85%) in our unit with respiratory disease in contrast to 56% of European neonates.

Our overall death rate (17·9%) was higher than in Europe (12·5%) but the comparison is more favourable when allowance is made for severity of illness (21·6% in the UK compared with 18·9% in Europe for classes 3 and 4). Among the sickest patients there were significant differences for mean and maximum TISS and physiological stability scores between survivors and non-survivors. This has been reported previously.[4 7–9] Schleffler *et al* demonstrated a complex relationship between survival and the level of therapeutic intervention in adults.[14] They observed that initially the probability of survival increases directly with the level of intervention and then decreases at the highest level of intervention, posing the dilemma that intervention can prolong life in the short term. We found no difference in stay in the intensive care unit between survivors and non-survivors and higher maximum scores than admission scores, confirming that the observation of Schleffler *et al* is equally valid for paediatric illnesses. As more resources are utilised by non-survivors the cost of their care is consequently greater. Our admission scores did show significant differences in points for physiological stability for outcome but not for TISS scores and two of the 11 patients who ultimately received treatment scoring 50 or more TISS points survived. Unfortunately there is no mortality predictor score available with the sensitivity to guide individual decision making[15] and efficiency of paediatric intensive care should not be maximised by patient selection on the basis of outcome.

In conclusion, the interest shown in paediatric intensive care in the UK has not been complemented by substantial evaluation. This study provides data that characterise the population of a typical multidisciplinary paediatric intensive care unit in terms of treatment options, sickness levels, resources utilised, and outcome. This information is important because not only is it necessary for meaningful clinical audit of ongoing activity within the unit but it also provides a basis for interunit comparisons of standards of care and outcomes. More information is essential and will be required by health service managers if the government's plans for competitive tendering of hospital services becomes a reality.

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Accidents on hospital wards

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Abstract

Eight hospitals reported 781 non-iatrogenic accidents occuring to patients and visitors under 16 years of age during an 18 month period up to October 1989. Accidents more often involved boys and children aged 3 to 5 years old. Falls from a height, slips, and striking accidents were common by day and falls by night. A total of 41% of accidents to inpatients occurred when parents were present. Only three accidents were serious. Altogether 27% involved beds and cots, and only one consequent injury was more than minor. Data collected routinely in case of medicolegal action can be presented in a form that may facilitate preventative work. Potentially remediable causes for concern include falls from beds and cots and the use of makeshift equipment.

Accidents are a frequent cause of mortality and morbidity to children, accounting for about 700 deaths and over one million attendances at accident and emergency departments every year.[1] Hospitals are generally considered to be places of safety where injuries are treated rather than generated. The problem of accidents occurring to children already on the ward has received little attention.[2–4] The atmosphere on children's wards is becoming more relaxed and parents are encouraged to participate in all aspects of the care of their child. It is to be expected that just as in the home, accidents may occur in the hospital setting in view of the additional dangers of mixed age groups at play together and heavy equipment. Although accident information is collected routinely in case of medicolegal action, with expenditure of both time and money, little use is made of these data for enhancing prevention. This paper proposes another approach whereby this might be achieved. The purpose of the study was to collect standardised information about accidents to children from a range of paediatric units, to identify major factors associated with accidents from this information, and to propose measures to reduce the frequency and severity of accidents. The study was exploratory and not designed to test hypotheses.

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Methods

A convenience sample of eight hospitals, varying from specialised paediatric hospitals accepting tertiary referrals to district hospitals with paediatric wards, was recruited. A questionnaire was circulated over an initial pilot period running from 1 June to 31 August 1988 and then over a full year from 1 November 1988 to 31 October 1989. The information collected concerned the accident, the injured person, the injury sustained, and the supervision of the child.

An accident was defined as 'an unpredicted event which potentially could lead to injury'. The subjects were inpatients or outpatients age 16 or under anywhere in the hospital including visitors. Iatrogenic events were specifically excluded.

Only descriptive analyses were performed. No formal hypotheses was tested in the analysis.

Results

A total of 781 questionnaires were analysed. Accidents to boys were commoner at all ages, and most accidents occurred to children under 5 years old (table 1).

Falls from a height were the commonest type of accident accounting for 42% of all cases. This was particularly noticeable for accidents during sleeping hours (table 2). The next category included being struck by, or coming into contact with, another person or equipment. There were also 11 scalds caused by hot drinks. Ten children were bitten by another child and one by a pet hamster. One entrapment was potentially fatal: a child of under 10 months was reported as having a bruised eye after being found trapped between the cot bars and the mattress.

Table 1 Age and sex distribution (number of cases)

Age	*Boys*	*Girls*	*Not known*	*Total*
1–<10 months	27	14	9	50
10–<19 months	62	42	13	117
19 months–<3 years	74	53	12	139
3–<5 years	117	67	2	186
5–<10 years	103	72	5	180
10–<16 years	60	36	6	102
Not known	—	—	—	7

Table 2 Accident types at different times (% of cases)

Time	*Fall*	*Struck*	*Slip*
08·00–11·59	38·5	26·9	27·4
12·00–15·59	34·7	30·0	25·3
16·00–19·59	32·4	30·7	25·7
20·00–23·59	52·3	20·0	18·5
00·00–03·59	90·3	6·5	3·2
04·00–07·59	62·0	21·1	11·3

Fall=fall from a height; slip=fall on one level.

Table 3 Type and severity of injury (number of cases)

Type	*Minor*	*Moderate*	*Severe*	*Total*
Bruise	227	12	3	242
Laceration	147	8	0	155
Burn	11	0	0	11
Bite	11	0	0	11
Fracture	0	2	2	4
Sprain	6	2	0	8
Overdose	0	0	1	1
Broken tooth	0	1	0	1
Epistaxis	3	0	0	3
Eye	2	0	0	2

The commonest result of an incident was no injury (338 cases). Bruises and lacerations were the commonest injuries (table 3).

The following accidents were serious. There were three cases involving contact with equipment resulting in bruising of children with either low platelet counts or haemophilia. There were two cases involving limb fractures, one after a three metre fall from a climbing frame, and the other in a child who was non-weight bearing as a result of a recent leg fracture. Finally one psychologically disturbed child took an overdose of antidepressant tablets (dothiepin 25 mg, 12 tablets). All these children required medical intervention.

Two fractures were reported as moderate: two cases of fractured skull, one when a child fell out of bed and the other when a visiting child fell off a chair. These two children required observation but not treatment.

The commonest site injured was the head (397 cases) (table 4). Thirty five individual locations were listed. Accidents varied in type according to their location (table 5).

Altogether 732 accidents occurred to patients, 302 (41%) while the child was in the presence of its parents. The remainder took place while nursing staff were supervising the child. Only two of these accidents involved outpatients, one in a day ward and the other in the *x* ray department. Forty nine accidents occurred to visiting children, 40 (82%) of whom were in the care of their parents and nine (18%) were unsupervised.

Twenty seven per cent of accidents involved beds and cots. Most of the associated accidents (78%) were falls and 52% occurred when parents were present. The skull fracture described above was the only more than minor injury to a well child after a fall from bed. The next most common equipment group was toys, which were responsible for 13% of equipment associated accidents.

Table 4 Site of injury

Site	*No of cases*
Head	397
None	80
Leg	52
Mouth	42
Arm	40
Back	38
Hand	38
Eye	29
Foot	21
Face	20
Abdomen	12
Chest	8
Internal	7
Shoulder	3
Labia	1

Table 5 Types of accident by location (% of total accidents in that location)

Location	*Fall*	*Struck*	*Slip*	*Poisoning*	*Bite*	*Total No*
Main ward	52·8	19·9	19·1	<1	<1	373
Cubicle	41·6	36·0	16·9	0	0	89
Side ward	54·9	23·9	11·3	0	0	71
Playroom	25·0	32·8	26·6	<1	6·3	64
External play area	35·6	26·7	31·1	<1	0	45
Ward corridor	11·6	39·5	48·8	0	0	43
Bathroom	10·5	26·3	52·6	10·5	0	19
Toilet	7·7	38·5	46·2	0	0	13

Discussion

This study had analysed information about a large number of accidents occurring in a hospital setting. Though many were trivial, they could readily have been more serious. Parents expect their child in hospital to be especially safe. Data about accidents are routinely collected but rarely used except in the case of medicolegal action. In this study, the data have been presented in a form that demonstrates the circumstances in which accidents are likely and could thereby form the basis of preventative work.

Frequency of accidents chiefly reflects exposure and it could be argued that injuries caused by the normal play and activity of children are difficult to avoid. Nevertheless, certain potentially remediable causes for concern can be identified.

A large proportion of night incidents were falls from a height and many equipment injuries involved cots and beds. Several of these falls were the result of the improper use of cot sides, that is, they were only half way up or incorrectly secured. This often happened in the presence of the mother. The correct use and the mechanism of hospital cot sides needs to be properly explained to parents and to junior nursing and medical staff. There are many different cot designs and staff must know how to operate the particular brands with which they are working. Another factor is the increased height of hospital beds compared with beds used at home. A possible solution would be the replacement of conventional beds with beds of adjustable height with an appropriate child resistant mechanism. These should be kept in the low position and raised only when required. Another consideration is the use of the correct bed for the child. Toddlers should clearly be in cots with sides. However, older children may just climb out, falling an extra metre in the process, and may be safer placed in a bed.

Other accidents might have been avoided by a better knowledge of child safety, for example, scalds from hot drinks and the entrapment between cot sides and the mattress. The latter also demonstrates the importance of using the correct equipment for the job and not makeshift arrangements, as has been previously shown for pacifiers.[5]

Nursing staff do receive basic information on safety during training, and it is a statutory requirement for them to be made aware of their responsibilities under the Health and Safety at Work Act (1974). During induction to the ward, however, these should be reviewed in a paediatric context. Training for medical, auxillary, and clerical staff could also be provided. This may best be carried out if it is the responsibility of a named individual, preferably a senior member of the ward staff.

Most accidents recorded in this study were trivial and this agrees with the results of others.[2 3] But this also suggests that if children present to accident and emergency departments with severe injuries and a history of a fall from a cot or bed, non-accidental injury should be suspected,[6 7] as the experience from this study is that such falls rarely have serious consequences.

We thank the nurse managers and nursing staff of the hospitals involved in the study: Royal Hospital for Sick Children Edinburgh, Royal Devon and Exeter Hospital, Westminster Children's Hospital, Royal Victoria Infirmary, Newcastle upon Tyne, The Children's Unit, Nottingham, Preston Royal Infirmary, Southampton General Hospital, and Whipps Cross Hospital. We also thank Miss Sue Burr of the Royal College of Nursing (RCN) and the RCN Nurse Managers Forum for advice, The Special Trustees of the Westminster and Roehampton Hospitals, Exeter Health Authority, Queen's Medical Centre, Nottingham, Harvey Scruton Ltd, The Grand Charity, and Sterling Health for funding the study.

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Medieval accidents

A medical historian at the College of Physicians of Philadelphia has looked at the chronicles of several English saints and martyrs to find out about childhood accidents in the middle ages (Eleanora C Gordon, *Medical History* 1991;**35**:145–63). There are, apparently, historians who have claimed that people in medieval times had no concept of childhood and lacked awareness of 'the particular nature of childhood'. Some assertions are inherently unlikely and when the roll call of daft ideas of the twentieth century comes to be read that one will surely rank as one of the daftest. It gains no support from the records of the hagiographers.

In the face of an emergency a common reaction was to call upon the help of a saint, promising a pilgrimage or a gift in return. Those who were in charge of the shrines of the saints would make careful records of the apparently miraculous tales told by the pilgrims and many of these records are still available, giving information about the kinds of mishap which befell people in those days. Dr Gordon has looked at the chronicles related to four saints and two revered 'near saints': St Thomas Beckett, St Wulfstan, St Thomas Cantilupe, St Edmund, Simon de Montfort, and King Henry VI. Covering the years 1170 to 1500 they give details of 135 accidents involving 134 children. Not surprisingly boys outnumbered girls by almost two to one and nearly a third of the children were under 3 years old. By far the most common type of accident was near drowning, accounting for 56% of the total. Head injuries occurred in about one in eight of the victims and choking, suffocation, or strangulation in a similar proportion.

The accounts give plentiful evidence of intense concern for the welfare of the children on the part of parents and neighbours but, of course, the series is highly selected, firstly because the children all recovered and secondly because only the more devoted parents would bother to make the pilgrimage after the child's recovery. There is, too, evidence that the foibles and behavioural characteristics of children of various ages were recognised and understood.

The misuse and ill treatment of children has, no doubt, always existed and attitudes to them have clearly varied from age to age but can there really ever have been an age when parents did not recognise 'the particular nature of childhood', the horrors of child labour and child abuse notwithstanding? Children are there to be observed; they must always have been observed. It can only be in the interpretation of their observations and in their reactions to them that adults in different ages have differed.

Returning to the late twentieth century, water is still a major hazard[1 2] and, of course, we have to cope with the car,[3 4] but in Britain at least we do not often have the carnage wrought by the gun.[5 6]

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Natural history of asthma in childhood—a birth cohort study

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Abstract

A cohort of 67 babies at risk of developing atopic disorders was followed up prospectively for 11 years. Clinical assessment and skin prick allergen sensitivity testing were performed annually over the first five years. At 11 years the cohort was restudied, symptoms were assessed by questionnaire, and bronchial reactivity (BHR) to histamine was measured. On the basis of skin testing, 35 children were atopic and 32 remained non-atopic. The expression of atopy increased with age. The lifetime prevalence of eczema, wheeze, and hay fever were 46%, 63%, and 56% respectively. The yearly period prevalence of hay fever increased with age, that of eczema declined, while that for wheeze showed a bimodal distribution with a peak before the age of 2 years and a gradual increase thereafter. Of the 21 children who wheezed before their second birthday, most never wheezed again and did not show BHR at 11 years. Of the 21 children whose first wheezing was after 2 years of age, 17 were still wheezing at 11 years and 12 showed BHR. Of the children who wheezed before 2 years of age, 10 were or became atopic, compared with 20 of the 23 children who wheezed at 11 years. These findings suggest that childhood asthma is a heterogenous condition with atopy being strongly associated with the persistence of wheeze.

Asthma affects at least 10% of school age children, yet despite this high prevalence there is much that remains unclear about the natural history of the disorder. Longitudinal studies of asthma in childhood are few and prospective information about preschool children is lacking from the British Cohort Study of 1958[1] and the long term follow up of wheezy children in Melbourne.[2] Although these workers have drawn attention to the differences between the preschool children who wheezed with viral infections and children with 'classical asthma', they concluded that children with recurrent wheeze and cough belonged to a single population with a common underlying defect.[3] This conclusion has recently been challenged on methodological and theoretical grounds.[4]

Recurrent wheezing in childhood has a strong association with atopy and this genetic abnormality is one of the strongest risk factors predicting whether a child develops asthma.[5 6] In an attempt to learn more of these variables we have conducted a prospective study from birth to 11 years in a cohort of children at risk of developing atopy. The study represents the continuation of the longitudinal investigation of recurrent wheezing in preschool children.[7–9]

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Subjects and methods

SUBJECTS

One hundred babies were selected for the study before birth on the grounds that one parent gave a history of hay fever or asthma. This selection was designed to provide a cohort of children of whom, on the assumption of an autosomal dominant inheritance, half would be expected to develop evidence of atopy, those without atopy acting as controls. In this study a stringent definition of atopy was taken as the presence of one or more positive skin prick tests (≥4 mm weal diameter) to common allergens. The study had the approval of the health district ethical committee. After full explanation, written consent was obtained from the pregnant mothers. All the babies were born in the maternity department of Poole General Hospital during 1977 and 1978. The cohort of 100 babies was initially studied for five years and later restudied when aged 11 years when all except one were prepubertal. As most of the families continued to live in the area served by the hospital there remained 92, 73, and 67 children in the cohort at 1, 5,[7] and 11 years respectively. The results presented in this report are on those 67 remaining children.

METHODS

All children were examined annually for their first five years and again when aged 11. The presence of eczema and wheeze was confirmed in all cases by a research nurse, a specialist, or a general practitioner during the first five years. A diagnosis of eczema was made when the skin of the face or of the flexures showed roughening, redness, or pruritus that persisted for four weeks or more. Hay fever was regarded as present if nasal discharge occurred in at least two spring or summer seasons. At the age of 11 years the diagnoses of hay fever and wheeze were based on a questionnaire administered to the patients inquiring into symptoms over the previous year and six years, while that for eczema was clinically confirmed.

Bronchial responsiveness to inhaled histamine was assessed at the age of 11 years in 66 children using the deVilbiss method.[10] After a saline challenge, increasing doubling doses of histamine were administered, followed at one minute by measurements of forced expiratory volume in one second (FEV_1) using a Vitalograph spirometer. The histamine dose was progressively increased until the FEV_1 fell by 20% of the post-saline (baseline) value. Children were considered to have hyperresponsive airways if this occurred up to or before the maximal cumulative dose of 7·8 µmol of histamine. The majority of children were challenged four times during the course of the year 1988/9 and were considered to have BHR if positive reaction occurred on one or more of the four challenges. Testing of the children was deferred if they had a history of a respiratory tract infection in the preceding month. In this age group the test has been shown to be repeatable to within a doubling dose.[11] [12]

The atopic states of the children were determined by skin prick testing to a panel of six allergens (*Dermatophagoides pteronyssinus*, mixed grass pollen, cat fur, dog dander, hens' eggs, cows' milk; Bencard UK Ltd), with a positive histamine and a negative control. This testing was undertaken by a standard technique at the ages of 1, 2, 3, 4, 5, and 11 years.[13] The same investigator performed these tests from the second year of follow up. A positive reaction was recorded if the mean diameter of the skin weal at 15 minutes was $\geqslant$ 4 mm more than a negative control; and the children were defined as atopic if they responded to one or more allergen at any age. At the final assessment the majority of parents were also skin tested to the same panel of allergens.

STATISTICS

Relative risks were calculated as the ratio of prevalence of a trait among exposed individuals to the prevalence of a trait among non-exposed individuals.[14] A relative risk of <1 suggests the exposure or trait may be protective, while >1 suggests an association, the higher the number the greater its strength. The significance was calculated by the χ^2 test and 95% confidence intervals were expressed. Smaller contingency tables were analysed by Fisher's exact test.

Results

On the basis of skin testing the total cohort of 67 children (31 boys) could be divided into 35 atopic and 32 non-atopic. The parents who had been selected on clinical grounds were subsequently shown to be atopic, with 10 false positives and 21 false negatives among the 115 parents who were skin tested.

The lifetime prevalence of eczema, wheeze, and hay fever was 46%, 63%, and 56% respectively. The number of children expressing atopy increased progressively with age: zero at 1 year two (3%) at 2 years, six (9%) at 3 years, 11 (16%) at 4 years, 14 (21%) at 5 years, and 35 (52%) by the age of 11 years. The yearly period prevalence of eczema declined, tending only to persist in the atopic children, that of hay fever increased occurring again mainly in atopic children, while that of wheeze showed a bimodal distribution with an early peak before 2 years and a gradual rise thereafter (table 1). Ten of the 21 children who wheezed before their second birthday were or became atopic, while 20 of the 23 children who wheezed at 11 were atopic ($p<0·01$). The majority of wheezy children did not present a major clinical problem, with only three having required hospital admission because of wheeze. Of the children who wheezed at 11 years (13 boys and 10 girls) eight were on regular medication (six inhaled β_2 agonists, three sodium cromoglycate, and four inhaled steroids). Sixteen (70%) of these children were sensitised to house dust mites, 12 (52%) to cats, and 10 (43%) to pollen. In contrast, of the 21 children who wheezed under 2 years of age (nine boys and 12 girls) only six (28%) became sensitised to house dust mites, five (23%) to cats, and six (28%) to pollen by the age of 11 years.

Bronchial hyper-responsiveness (BHR) to histamine was seen in 23 of the children at 11 years, of whom 21 were atopic, 17 had wheezed in the previous year, and three of the remaining six had previously had a recorded episode of wheeze. The degree of BHR was related to the child's atopic status; the two non-atopic children required greater than 1·8 µmol of histamine to respond, compared with the 16 of the atopic children who responded to less than this dose ($p<0·001$). The relative risk of a child wheezing before his or her second birthday, wheezing at 11, or showing BHR at 11 was calculated (table 2). There was no association between atopy and wheezing in infancy, but it was strongly associated with wheeze at 11 years of age.

The natural history of wheeze was dependent on the age at the first wheeze (figure). Of the 21 children whose first wheezing episode was under 2 years of age, 16 (76%) were wheeze free, and 13 (61%) did not show BHR, at 11 years; that is, there was only a 1 in 4 chance of wheezing at age 11. Four of the five infants whose wheeze persisted were atopic and showed BHR. Among this subgroup were the three children who had required hospital admission, were on regular inhaled steroids, showed BHR to $<0·98$ µmol of histamine, and were considered the 'worst' asthmatics of the cohort. The one non-atopic child did not show BHR and was on no medication. These five children could be distinguished clinically during infancy by the greater frequency of their wheezing episodes: they had three or more each year while most of the other children had only

Table 1 Yearly prevalence of children with wheeze, eczema, and hay fever from the total cohort of 67

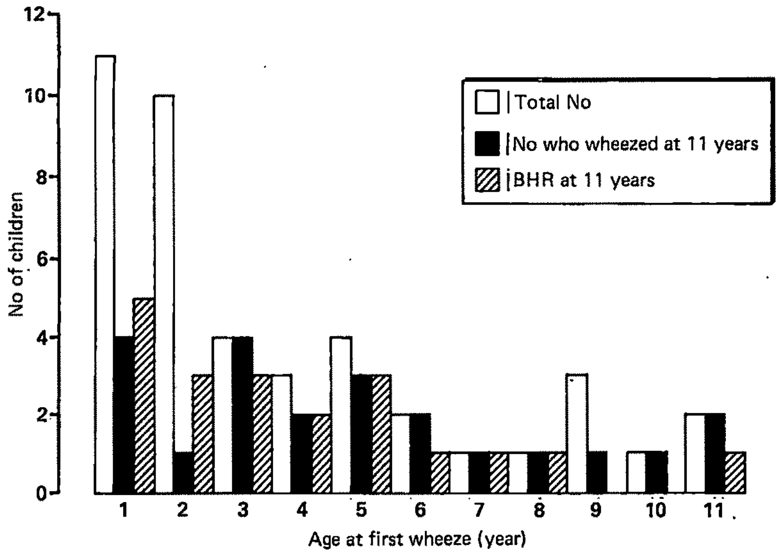
	Age (years)					
	Birth–1	1–2	2–3	3–4	4–5	10–11
Wheeze						
Total	11	15	7	10	16	23
Atopic†	6*	7**	6	7	11	20
Eczema						
Total	15	23	8	7	6	1
Atopic	8	12	4	5	5	1
Hay fever						
Total	‡	3	2	10	11	27
Atopic	—	2	2	9	9	22

†Atopy was defined as those children who had a skin weal $\geqslant$ 4 mm to an allergen during childhood.
*$p=0·05$, **$p<0·01$ for the comparison with the number of atopic children to non-atopic children wheezing at 11 by Fisher's exact test.
‡Excluded by definition.

Table 2 Relative risk (95% confidence intervals) of children having atopy, wheeze at 0–2 years, wheeze at 11 years, bronchial hyperreactivity (BHR) at 11 years

	Atopy	*Wheeze 0–2 years*	*Wheeze at 11 years*	*BHR at 11 years*	*Wheeze + BHR at 11 years*
Wheeze 0–2 years (n=21)	0·9 (0·5 to 1·5)	— —	0·6 (0·3 to 1·3)	0·9 (0·4 to 2·0)	0·9 (0·4 to 2·2)
Atopy (n=35)	— —	0·8 (0·4 to 1·6)	6·1*** (2·5 to 14·4)	10·0*** (3·8 to 25·5)	14·6*** (3·9 to 54)
		Positive skin test at 11 years			
House dust mite (n=25)	— —	0·7 (0·3 to 1·5)	4·2*** (2·0 to 8·6)	4·4*** (2·2 to 8·8)	5·3*** (2·3 to 12·6)
Cat dander (n=20)	— —	0·6 (0·2 to 1·3)	3·4*** (1·8 to 6·5)	4·4*** (2·3 to 8·3)	4·5*** (2·1 to 9·9)
Mixed pollen (n=18)	— —	1·4 (0·6 to 2·9)	2·1* (1·0 to 4·0)	3·9*** (2·0 to 7·3)	6·0*** (2·4 to 15·1)
		Skin reaction in infancy			
Egg (n=14)	1·7* (1·1 to 2·8)	1·0 (0·5 to 2·3)	2·0* (1·0 to 4·0)	2·3* (1·2 to 4·6)	2·9** (1·3 to 6·3)

*p<0·05, **p<0·01, ***p<0·001. All other values were not significant p>0·05.



Age at the first wheeze (year) and the subsequent presence of wheeze and bronchial hyper-responsiveness (BHR) at 11 years of age.

one or two episodes. In contrast to the 21 children whose first wheezing episode was after their second birthday, only four (19%) were wheeze free at 11 years of age (p<0·001) and nine (43%) did not show BHR (not significant); that is, the chance of wheezing at 11 was 4 in 5.

Discussion

This prospective study of children born of atopic parents, and therefore at risk of atopic disease, has shown the number of children expressing their atopic status and the prevalence of atopic disease increases with age. It is estimated that in the UK 50% of couples have an atopic member so a large proportion of children would have a similar atopic pedigree as those in this small cohort study. The definition of atopy used was an objective one using allergen skin prick testing to demonstrate immediate hypersensitivity. A skin weal size of 4 mm greater than the negative control was arbitrarily chosen as there were clear examples of children losing all skin reactivity to allergens when a less stringent threshold was used. The validity of this definition was supported by both the strong association of positive skin tests in the children and allergic disease and the close correlation between allergic symptoms and subsequent skin testing in their parents.

Under 2 years of age we have identified a peak of children who had their first wheezing episode. Many of these very young children wheezed only once. On a nine year follow up the natural history of wheeze in these children differed from those who started to wheeze after their second birthday. This is in keeping with a study from a general practice which found that the earlier a child wheezed, the better the prognosis. It was also found that the parental recall of wheezing in infancy was increased if later respiratory problems occurred.[15] This bias resulted in an overestimation of the number which progress to persistent wheezing in later childhood and may explain the differences between the findings in prospective and retrospective studies.

It seems likely that respiratory viral infections have an important part to play in the production of wheeze in young children. Positive viral isolates have been made in several studies,[16 17] although in earlier reports of the present cohort there was little success at culturing virus during episodes of wheeze.[9] It is possible that the effects of infection on the smaller calibre airways of infants is sufficient to produce clinical wheeze; indeed, a prospective study has shown that infants with reduced lung volumes are more prone to wheeze.[18] In the older children it is those who were atopic and, as a consequence, capable of developing immediate hypersensitivity, who had persistent wheeze and hyperreactive airways. There was no evidence to support the theory that viral infections in infancy influenced the subsequent development of atopy. It has been suggested that all wheezy children belong to a homogenous group with a similar genetic background.[3] However, evidence from this longitudinal study of children with a similar genetic background suggests that there are at least two groups of wheezy children, one group who progress to develop 'asthma' in later childhood and another who do not develop atopy and do not wheeze again.

We understand atopy to be an inherited

trait,[19 20] which is expressed after prolonged allergen exposure.[21] Our findings confirm cross sectional studies showing that atopy is strongly associated with childhood asthma.[5 6] An important finding in this study based on the general population was that the prevalence of wheeze had not declined by 11 years, which is in contrast to findings of previous studies.[22 23] Contrary to popular opinion,[24] this study has not confirmed that infantile eczema, based on our clinical definition, was a useful predictor of atopy as many non-atopic children were affected. This supports the observation that it is frequently confused with seborrhoeic dermatitis.[25] Our most useful early predictor of atopy was a reaction (weal size greater than 2 mm) to egg on skin testing (sensitivity 78%, specificity 54%).

This longitudinal study of children at risk of atopy has shown that it is those children who develop immediate hypersensitivity who are more likely to have persistent symptoms of wheeze and that the risk of a child whose first episode of wheeze is before 2 years of age continuing to wheeze at 11 is low. We interpret these findings to suggest that heterogenous mechanisms operate in the causation of wheeze at different ages.

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Lipoprotein (a) concentrations as risk indicators for atherosclerosis

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Abstract

The plasma concentration of different lipoproteins were measured in 102 control children, in 42 children with a parent suffering from coronary heart disease (CHD), and in 50 children with a parent with cerebrovascular disease (CVD). Significant differences between controls and children in the other two groups were found for apolipoprotein A I, apolipoprotein B, and high density lipoprotein-cholesterol. Children of parents with CHD differed from controls in total cholesterol and apolipoprotein A II concentrations. A highly significant difference furthermore was found in lipoprotein (a) concentrations from children of parents with CHD in comparison with controls, but not between children of parents with CVD and controls. The difference in lipoprotein (a) concentrations (children of parents with CHD compared with controls) were only noticed in children above the age of 10 years. This could be explained by the observed rise of lipoprotein (a) between age 2 and 13 years, which was much more pronounced in the group with parents who had CHD. Plasma glycosaminoglycan concentrations were also measured in the three groups. They were significantly higher in children of parents with CHD and CVD compared with controls; they also varied with age.

The pathophysiological events leading to atherosclerosis are known to originate already in early childhood.[1] In numerous reports multivariate analysis of prospective morbidity and mortality studies strongly suggest a family history for coronary heart disease (CHD) and cerebrovascular disease (CVD). In fact it appears that genetic and familial factors contribute most to the risk of atherosclerosis.[2] As the causes for atherosclerosis are multifactorial, there is no single parameter that would allow prediction of the individual risk with sufficient certainty. Evidence is accumulating, however, that raised plasma lipoprotein (a) concentrations contribute to a great extent to atherogenesis especially if low density lipoprotein-cholesterol is increased in addition.[3–6] In a previous study we investigated 1500 young soldiers and based on a questionnaire they were divided into two groups: positive and negative family history of myocardial infarction. It was found that parents of children with premature myocardial infarction had significantly higher plasma lipoprotein (a) concentrations compared with healthy controls.[7]

In this study we extended our previous work by investigating the children of people suffering from CHD and CVD separately. The data are not based on a questionnaire but derive from blood analysis of the children of affected patients directly.

Previous in vitro experiments in our laboratory, aimed at shedding more light on the possible molecular mechanism of the atherogenicity of lipoprotein (a), demonstrated that this lipoprotein avidly complexes with glycosaminoglycan, and this in turn is recognised by the scavenger receptors on macrophages.[8] Such a process may favour the complex formation of lipoprotein (a) with intracellular matrices of arteries, followed by triggering of the onset of early lesions. As it is known that glycosaminoglycan is present in a variable concentration in circulating blood even in healthy people, we measured glycosaminoglycan concentrations in the serum of children and correlated them with age and familial atherosclerosis risk.

Subjects and methods

Ninety six children with an established familial risk for atherosclerosis between 2 and 15 years of age were investigated and compared with 102 control children matched for age and sex. This control group consisted of children who were admitted to hospital for various reasons not connected with acute diseases or metabolic defects, for example, tonsillectomy.

The children at risk for atherosclerosis were divided into two groups: (1) those with a parent suffering from CHD (a myocardial infarction at <45 years of age) (n=46) and (2) those with a parent suffering from CVD who had had a stroke and apoplexia (n=50).

Blood was collected from children during a period of absence of any virus or other infection, after an overnight fast, and it was allowed to clot at room temperature for 1 hour. The serum was separated by centrifugation at 1500×*g* for 15 minutes.

The concentration of plasma lipids was measured enzymatically by routine laboratory methods. Lipoproteins and apolipoproteins were quantified immunochemically as described previously.[4 7 8] Lipoprotein (a) was quantified using ready to use Laurell plates, as well as standards from Immuno Diagnostica. The concentration of glycosaminoglycan in serum was estimated by measuring the hexuronic acid concentration.[9]

STATISTICAL ANALYSIS

For comparison of all three groups with each

Table 1 Mean (SD) concentrations of different parameters measured in the serum of high risk children of parents with CHD and CVD in comparison with age and sex matched controls

	Total cholesterol (mmol/l)	*Triglyceride (mmol/l)*	*High density lipoprotein-cholesterol (mmol/l)*	*Apolipoprotein A I (g/l)*	*Apolipoprotein A II (g/l)*	*Apolipoprotein B (g/l)*	*Glycosaminoglycan (mg/l)*
CHD (n=46)	4·87 (0·93)*	0·94 (0·26)	1·01 (0·27)*	1·41 (0·22)*	0·41 (0·06)*	0·61 (0·19)*	13·2 (6·9)*
CVD (n=50)	4·30 (0·78)	0·88 (0·21)	1·04 (0·25)*	1·40 (0·17)**	0·42 (0·06)	0·63 (0·21)**	13·2 (3·3)**
Controls (n=102)	4·35 (0·65)	0·84 (0·23)	1·15 (0·22)	1·49 (0·17)	0·44 (0·05)	0·50 (0·14)	11·0 (2·5)

Significantly different from controls: *$p<0{\cdot}05$ and **$p<0{\cdot}01$.

Table 2 Quartile concentrations of lipoprotein (a) in mg/l in serum of high risk children of parents with CHD and CVD in comparison with age and sex matched controls

	Q_{25}	Q_{50}	Q_{75}
CHD (n=46)	60**	126**	397**
CVD (n=50)	25	80	196
Controls (n=102)	17	75	138

**Significantly different from controls: $p<0{\cdot}01$.

other the one way analysis of variance was used for normally distributed variables and the Kruskal-Wallis H test for non-normally distributed variables. Comparison of two groups was performed by the Student's *t* test or the Wilcoxon Mann-Whitney U test respectively using a Bonferroni correction for multiple testing as described in detail earlier.[6]

Results and discussion

Table 1 shows mean (SD) concentrations of some of the lipid and lipoprotein parameters of the two high risk groups of children in comparison with controls. There was no significant difference in triglyceride concentration in the two high risk groups in comparison with controls. Highly significant differences were found in the concentration of apolipoprotein B, which was higher in the two high risk groups compared with controls. Apolipoprotein A I and high density lipoprotein-cholesterol were significantly different between both high risk groups and the control group. A significant difference ($p<0{\cdot}05$) in the apolipoprotein A II concentrations was also noticed between the group with a parent who had CHD and the control group.

Because of the non-normal distribution of lipoprotein (a) medians for serum concentration were calculated and the Kruskal-Wallis statistics were used for calculating differences.[6] As can be seen in table 2 median lipoprotein (a) serum concentrations were highest in the group with a parent who had CHD and lowest in the control group. The differences were significant ($p=<0{\cdot}01$). There was no significant difference in median values of lipoprotein (a) between children with a parent who had CVD and control children.

In a previous study of a large family where serum lipoprotein (a) concentrations of three different generations were investigated, we showed that lipoprotein (a) increases with age.[10] In another study we also found that newborn babies have very low lipoprotein (a) concentrations which slowly increase in the first weeks of life. In order to account for these fluctuations, lipoprotein (a) concentrations of the group with a parent with CHD and the control group were plotted against age (fig 1). Significant differences between these two groups could be established above the age of 10 years only. Maximal differences were apparent at the age of 13 years. On the basis of earlier findings of our group as well as of others, it seems well documented that lipoprotein (a) concentrations >300 mg/l are significantly correlated with premature atherosclerosis and myocardial infarction.[3–6] From data in the present study it appears that this cut off concentration may be much lower in children below the age of about 10 years. We also conclude on the basis of the present study that lipoprotein (a) might be a significant discriminator for CHD only if measured in children of about 5 years or older.

We also measured the serum concentrations of glycosaminoglycan in the different groups and plotted them against age (fig 2). In all age groups the concentrations were significantly higher in both groups of high risk children in comparison with control children. As concentrations of glycosaminoglycan in both groups of

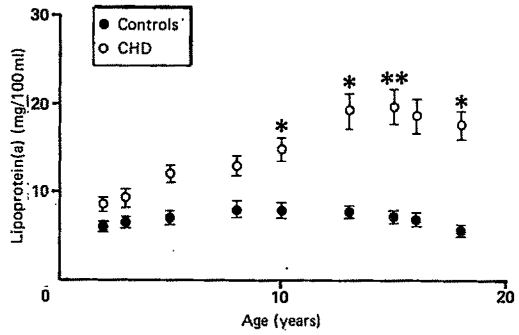

*Figure 1 Age related changes in concentrations of lipoprotein (a) in children of parents with CHD and controls; *$p<0{\cdot}05$.*

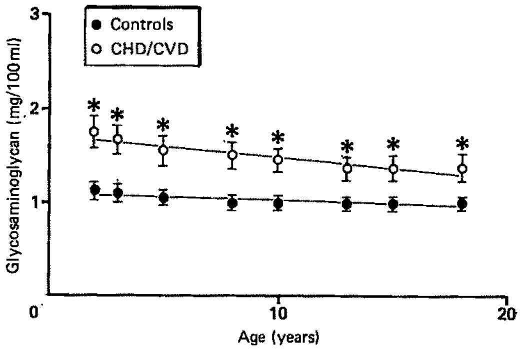

*Figure 2 Age related changes in concentrations of glycosaminoglycan in children of parents with CHD and CVD and controls; *$p<0{\cdot}05$.*

high risk children were not significantly different from each other, they were combined in fig 2. The highest differences were measured in children with a parent with CVD below the age of 5 years. These findings suggest that serum concentrations of glycosaminoglycan in fact correlate positively with the incidence of vascular diseases, and that individuals with extremely high serum concentrations might be prone to CVD. This hypothesis of course needs to be verified in longitudinal studies with a much larger sample size. Whether or not the differences in concentrations of glycosaminoglycan are of genetic or of environmental origin is not clear yet and this is currently under investigation in our laboratory. Another open question that awaits clarification is whether or not increased concentrations of glycosaminoglycan persist until adulthood. These questions with respect to lipoprotein (a) seem much more clear. From earlier work we know that lipoprotein (a) concentrations are genetically determined and increase with age.[6 9 10] There are also indications that the patterns of plasma lipoproteins in general and that of lipoprotein (a) in particular differ between adult patients with CHD and those with CVD.[11] These earlier findings are strengthened by this study.

In conclusion we have shown that children with a familial risk for atherosclerosis do in fact differ in several parameters from control children. Children of parents with CHD exhibit significantly raised concentrations of lipoprotein (a) and apolipoprotein B, reduced high density lipoprotein, and increased values of serum glycosaminoglycan. The children of parents with CVD exhibited similar changes in serum lipoproteins and glycosaminoglycan; lipoprotein (a) concentrations, however, were not different from controls.

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Panniculitis: a report of four cases and literature review

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Abstract

Panniculitis is a disease with many causes and associations. The classification of clinical subtypes is unsatisfactory and hampered by the use of eponyms.

Four children with recurring panniculitis are described and their histology presented. Three had subcutaneous fat atrophy with lobular panniculitis on biopsy; all responded well to corticosteroids. The fourth child had a septal panniculitis with no atrophy of subcutaneous tissues and only a partial response to treatment with corticosteroids.

A widely accepted precise histological classification of panniculitis is needed to enable accurate predictions of the outcome of this serious disorder.

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Panniculitis is an uncommon but fascinating condition in childhood. Inflammation of the fat may arise spontaneously or occur as a feature of distinct illnesses such as pancreatitis,[1] bacterial septicaemia,[2] systemic lupus erythematosis,[3] polyarteritis,[1] and malignancy.[4] The literature abounds with isolated case reports using eponyms such as 'Weber–Christian syndrome'[5] and 'Rothman–Makai panniculitis'.[6] Although attempts have been made to classify histological subtypes of panniculitis,[1 7] no universally recognised classification is in use to aid retrospective studies. The various forms of lipodystrophy are often included in the classification of panniculitis,[8] which then becomes further confused.

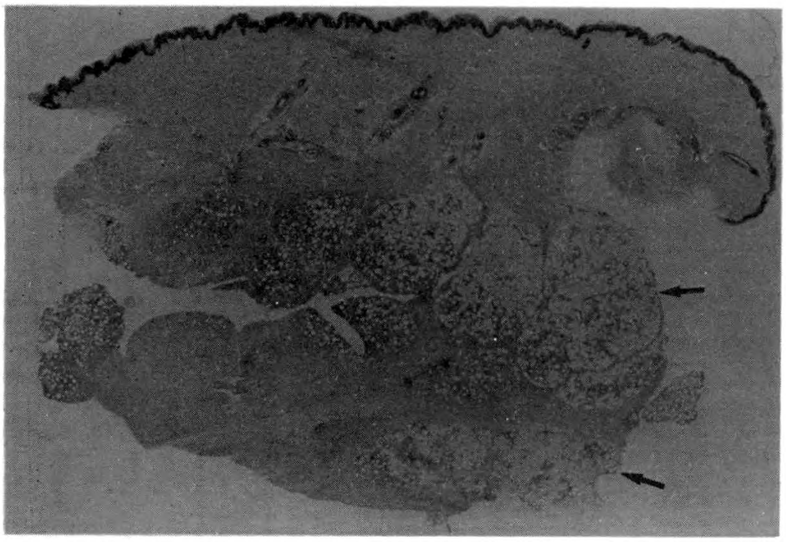

Figure 1 Case 1: histological appearance of lobular panniculitis (arrows). (Haematoxylin and eosin stain × 10.)

We report four cases of spontaneously occurring panniculitis, one in an infant and three in older children. Follow up of our four children over several years suggests that lobular panniculitis is associated with significant fat atrophy at the site of previously active lesions and a good response to corticosteroids. Septal panniculitis, however, has no associated atrophy of fat and only a partial response to corticosteroids.

Case reports

CASE 1

A 6 year old girl first presented in 1975 with an upper respiratory infection and painful lumps on both thighs. Both problems resolved spontaneously. The painful lumps reappeared three years later and biopsy specimen of a nodule demonstrated lobular panniculitis (fig 1).

Other investigations included a haemoglobin concentration of 94 g/l, total white cell count of $11\cdot9\times10^9$/l, erythrocyte sedimentation rate (ESR) of 60 mm/hour, a significant rise in antistreptolysin 0 titre (ASOT) over two months, a positive rheumatoid factor, and raised immune complexes. Serum C3 concentration was 1·65 g/l (normal range 0·8–1·70 g/l) and C4 0·23 g/l (normal range 0·15–0·45 g/l). Serum IgG was 28 g/l (normal range 6·5–16·5 g/l). Direct Coombs test, the Venereal Disease Research Laboratory test, *Treponema pallidum* haemagglutination assay, and tests for antinuclear and anti-DNA antibodies gave negative results. No cryoglobulins or cold agglutinins were detected, and serum IgA, IgM, euglobulin lysis and fibrin plate lysis were normal.

Prednisolone was given in a dose of 30 mg/day orally from January 1979 tapering to 30 mg and 5 mg on alternate days by February 1979. The prednisolone dose was steadily reduced over the next five months, ceasing in July 1979 at which time there was resolution of the lesions with appreciable loss of subcutaneous fat at the sites of the previous nodules. The nodules reappeared three months after cessation of treatment. Treatment with prednisolone was again successful in controlling the symptoms when given in a dose of 30 mg/day orally, initially, and decreased steadily as before over the next nine months until ceasing in July 1982. Currently the child remains well and free of new lesions.

CASE 2

This girl was completely normal until the age of 5 months when she developed red hot lumps on both legs. By 16 months of age the lesions had spread to involve her face, arms, and trunk. There were no systemic symptoms. A skin biopsy specimen showed a septal panniculitis (fig 2) that responded temporarily to prednisolone in small doses.

At 3·5 years of age she developed fever, joint pains, and stiffness with increasing numbers of nodules appearing after bouts of tonsillitis. A trial of prophylactic penicillin decreased the number of infections but did not appear to modify the disease process.

Subsequent treatment included chloroquine, indomethacin, naproxen, and sulphasalazine; none of these drugs resulted in any lasting benefit. Prednisolone was used in small doses (for example, 5 mg) daily until the age of 5·5 years when alternate day treatment was begun up to a dose of 20 mg at 11 years old. Increases in prednisolone dose led to partial improvements but relapses still occurred (fig 3). Temporary improvement was seen after three pulses of intravenous methylprednisolone were given in response to an acute exacerbation of the disease. Dapsone was started at 13 years of age with some improvement of fevers and nodules.

During the course of this girl's illness her haemoglobin has remained at 100–111 g/l and her ESR has ranged from 13 to 30 mm/hour.

Tests for antinuclear antibody, immune complexes, autoantibodies to gastric parietal cells, smooth muscle, mitochondria, reticulin and thyroglobulin gave negative results. ASOT, throat swab, and urine and blood cultures were also negative. Plasma urea, electrolytes, C reactive protein, triglycerides, cholesterol, red cell folate, serum complement, immunoglobulins, and B12 concentrations and bone marrow examination were all normal.

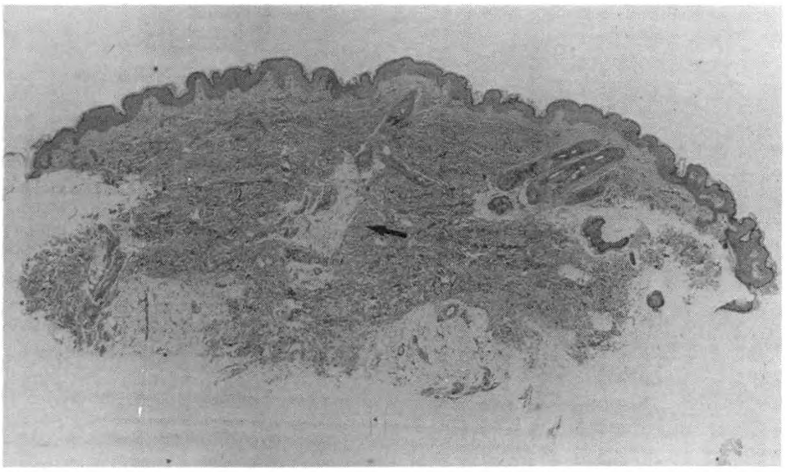

Figure 2 In contrast to fig 1 this biopsy shows relatively normal fat lobules with inflammation of the surrounding septa (arrow). (Haematoxylin and eosin stain × 10.)

CASE 3

In December 1985 an 11 year old girl developed painful erythematous indurated lesions over her feet and legs (fig 4) after recovering from a sore throat. She was not febrile but appeared lethargic. At the same time the metatarsophalangeal joints of both feet were tender.

There was no improvement with penicillin, aspirin, other non-steroidal anti-inflammatory drugs, and bed rest. Her haemoglobin concentration was 113 g/l, white cell count $6 \cdot 8 \times 10^9$/l, and ESR 60 mm/hour. Rheumatoid factor was positive (RAHA 1:1280) initially, becoming negative by November 1987. Plasma C reactive protein was 27 000 μg/l (normal <8000). The

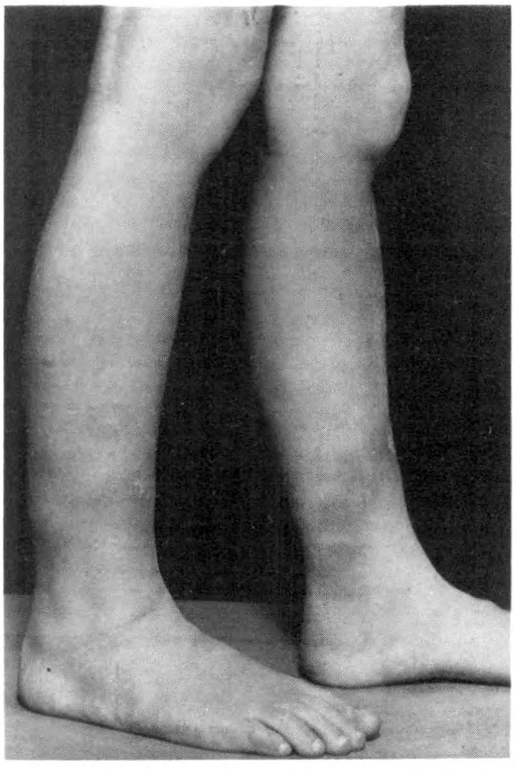

Figure 3 Case 2: calf nodules of septal panniculitis in relapse.

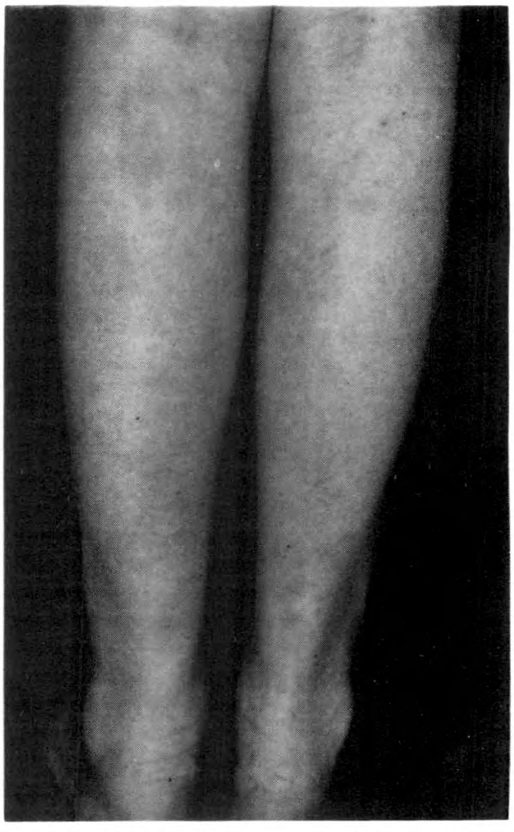

Figure 4 Case 3: swelling and erythema of the legs in the acute phase of lobular panniculitis.

plasma urea and electrolytes, liver function tests, amylase activity, ASOT, serum immunoglobulins and complement, urine analysis, nose and throat swabs, and chest radiography all gave normal results. Autoantibodies to parietal cells, mitochondria, smooth muscle, reticulin, thyroid microsomes, and thyroglobulin were not detected. Antinuclear and anti-DNA antibodies were negative and antibodies to extractable nuclear antigen were not detected.

One month after onset of the illness nodules began to appear on the child's arms. A skin biopsy specimen demonstrated lobular panniculitis and prednisolone was started at a dose of 40 mg alternating with 10 mg daily. She became more energetic and the skin lesions gradually resolved, leaving large areas of subcutaneous fat loss (fig 5). Prednisolone intake was cautiously reduced as three small lesions persisted and occasional lesions appeared at sites of minor skin trauma. By August 1988 the prednisolone dose was 25 mg on alternate days, the child felt well, and the ESR had fallen to 6 mm/hour.

CASE 4

A girl weighing 4500 g was born by elective caesarean section after a normal pregnancy in August 1985. She had signs of ventricular and atrial septal defects leading to congestive cardiac failure by 5 weeks of age. Corrective cardiac surgery was performed three weeks later after medical treatment had failed to control her condition.

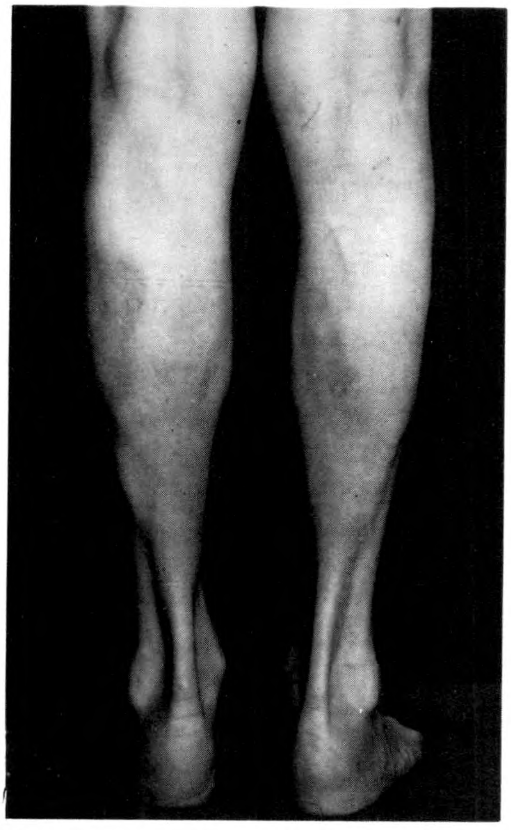

Figure 5 Case 3: appreciable subcutaneous fat loss seen after resolution of the acute inflammatory stage of lobular panniculitis.

Postoperatively the baby required intensive respiratory and cardiovascular support but was able to go home after two weeks in hospital. Shortly afterwards she developed red tender lumps on her trunk, thighs, arms, and scalp. These lumps resolved spontaneously but reappeared five weeks later on the baby's arms, shoulder, and face where they were sufficiently tender to interfere with feeding.

A biopsy specimen of an active lesion showed lobular panniculitis that responded well to prednisolone in a dose of 1·5 mg/kg/day. The dose of steroid was reduced over the next five months and there has been no recurrence of disease off treatment.

Investigations at the time of biopsy showed a haemoglobin concentration of 95 g/l, white cell count of $12{\cdot}2\times10^9$/l, and an ESR of 13 mm/hour. ESR at presentation was 40 mm/hour. Serum amylase and creatine phosphokinase activities and ASOT were normal. No immune complexes were detected.

Discussion

Our four cases demonstrate the two histological types of panniculitis previously described, lobular and septal.[1] Although these types have been recognised in the past no attempt has been made to correlate histological type with response to treatment. Our review of the literature supports this paper's finding that lobular panniculitis responds better to treatment with prednisolone than the septal type.

Two of our children were infants at the onset of the illness. Most of the infants described previously have had significant systemic symptoms and in some cases a fatal outcome.[6] Our infant with lobular panniculitis has done well on steroids alone. She now has no fat atrophy and is off treatment with no recurrences. Taylor[9] and more recently Conway *et al*[10] have also described cases of panniculitis with onset in infancy where the clinical course has been relatively mild and there has been a good response to treatment. Our child with septal panniculitis whose disease began at 5 months of age, although still having problems, has not succumbed and has not developed symptoms of perivisceral disease.

The nature of the inflammatory infiltrate found on histology varies according to the disease stage at which the biopsy is performed.[11] It is important to obtain adequate biopsy specimens early in the disease as once the end stage is reached, subcutaneous fibrosis of the panniculis may be all that is seen and the lobular architecture of the fat is distorted. Punch biopsies are not recommended because they may not obtain adequate samples of fatty tissue because of inflammation of the subcutaneous tissue, which leads to decreased adherence of the dermis to the fat in the early stages.[1]

Unless an acute lesion is biopsied histology can be meaningless so that children presenting with a loss of subcutaneous fat are particularly difficult to diagnose. In the four patients described by Peters and Winkelmann nodules were not present at the beginning of the disease or if present were obvious only briefly.[12] Three of their patients were thought to have lipodystrophy until biopsies showed panniculitis.

Upper respiratory tract infections preceded the panniculitis in two of our cases with lobular panniculitis. The child with septal panniculitis suffered frequent exacerbations of her disease after bouts of tonsillitis as did a child with lobular panniculitis described by Gupta and Rasmussen.[13] Septal panniculitis has been recently associated with Lyme disease.[14] There is a similarity between this form of panniculitis and erythema nodosum. Erythema nodosum is considered to be a hypersensitivity reaction to a variety of antigenic stimuli and is seen during several infectious diseases including those caused by β haemolytic streptococci. It is clear from the literature that the presence of infection is not predictive of the histological type of panniculitis nor the clinical outcome.

The infant who underwent corrective cardiac surgery was initially thought to have 'cold panniculitis' resulting from the hypothermia during surgery. A recent case report describes an infant with similar problems after cardiac surgery and the diagnosis of subcutaneous fat necrosis of the newborn was made on the histological findings.[15] Cold panniculitis has previously been described but is localised to the area affected by the hypothermia, begins hours to at most a few days after the insult, and does not spontaneously recur without further exposure to cold.[16] Our child's lesions recurred too long after cardiac surgery to be consistent with cold panniculitis. Nor is this child's condition compatible clinically or histologically with sclerema neonatorum or subcutaneous fat necrosis of the newborn.

Immunological abnormalities have previously been reported in association with panniculitis. Allen-Mersh described a 7 year old girl who first presented with a panniculitis of the foot and who then went on to develop diabetes mellitus, hepatic cirrhosis, red cell surface antibodies, and antibodies to mitochondria and gastric parietal cells.[17] Recently Billings *et al* reported three cases of lobular panniculitis.[18] One of the patients had insulin dependent diabetes and Hashimoto's thyroiditis, the second later developed juvenile chronic arthritis, and the third insulin dependent diabetes.

Hendricks *et al* describe a child whose disease began after immunisation and another who did not develop new lesions while he was lymphocyte depleted.[6]

Our two older children with lobular panniculitis had positive rheumatoid factors. One had a raised ASOT and immune complexes. All children had negative autoantibody screens. The significance of these isolated findings is not clear and a review of the literature does not suggest any correlation between the nature of the immunological disturbance and the histological type of panniculitis.

It is clear that many factors are involved in the initiation of panniculitis. It is possible that various physical and chemical agents and infections expose parts of the lipocyte increasing its vulnerability to attack by autoimmune mechanisms. This is supported by the increased incidence of panniculitis among children with α_1-antitrypsin deficiency.[19]

Steroids have been the mainstay of treatment of panniculitis but some children do not respond.[20] Other agents tried with success have been chloroquine,[21] [11] azathioprine,[10] cyclophosphamide,[22] and more recently dapsone.[23] [24]

Panniculitis is a disease with at least two distinct histological subtypes. Current treatments are often based on the results presented in numerous case reports rather than the outcome of prospective trials of treatment. The incidence of panniculitis is low but for a particular child this illness may cause serious disability or even death. It is for these reasons it is suggested that all children who present with recurrent painful nodules of panniculitis have an early and adequate biopsy to ascertain the histology. Prompt treatment may prevent further severe illness as well as disfiguring subcutaneous fat loss.

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Reference:
1. Livingston J *et al* (1989) Br J Clin Pharm 27 (Suppl 1): 1095 –1125

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Archives of Disease in Childhood 1991; **66**: 1061–1064

Effect of salbutamol on oxygen saturation in bronchiolitis

Ling Ho, G Collis, L I Landau, P N Le Souef

Abstract

Inhaled sympathomimetic agents are often used in bronchiolitis with little objective evidence of benefit. The arterial oxygen saturation (Sao_2) reflects the adequacy of ventilation-perfusion balance. The aim of the current study was to determine the effect of inhaled salbutamol on Sao_2. In a randomised, double blind study, 21 infants, admitted with bronchiolitis positive for respiratory syncytial virus, had continuous Sao_2 measurements made before and after nebulised salbutamol or placebo. Sao_2 was recorded over 30 minutes for a baseline, then during the 10 minutes of first nebulisation with either salbutamol or saline, then over 30 minutes after nebulisation, the 10 minutes of second nebulisation with the alternate regime, and another 30 minutes after this second nebulisation. Desaturation occurred after salbutamol and saline nebulisation. The fall in Sao_2 with salbutamol was seen whether infants received it as the first or second nebulisation. The fall in Sao_2 after saline was seen when given first, but not when given after salbutamol. The decrease in Sao_2 was greater and more prolonged with salbutamol than with saline. Routine nebulised aerosol sympathomimetic treatment during acute bronchiolitis cannot be recommended.

Acute bronchiolitis in infants is a common cause of hospitalisation. The use of bronchodilators in respiratory viral bronchiolitis has been controversial.[1-3] Studies during the acute and the recovery phase of bronchiolitis have shown variable change in respiratory resistance and work of breathing with some demonstrating increased hypoxia after a single dose of nebulised sympathomimetic.[1-24] Improved conductance in some infants has been reported.[9] Conflicting results from the limited measurements possible in this young age group and entrenched preconceptions still lead to uncertainty about the role of bronchodilators in the treatment of acute bronchiolitis.

Arterial oxygen saturation (Sao_2) is the most relevant outcome measurement of the adequacy of ventilation and ventilation-perfusion balance. We measured the effect of aerosol sympathomimetics on continuous Sao_2 measurements in infants with acute viral bronchiolitis.

Subjects and methods

SUBJECTS

Children admitted with cough and wheeze due to acute bronchiolitis were entered into the study within five days of admission. All children had no prior history of respiratory symptoms, the clinical findings of hyperinflation with wheeze and crackles on auscultation, and respiratory syncytial virus isolated by immunoflourescence of a postnasal aspirate. Severely ill children and those with associated chronic disabilities were excluded. Approval was obtained from the hospital's medical ethics committee and parental consent was obtained. The children were studied while quiet without sedation.

We studied 21 infants; there were 11 boys and 10 girls with a mean age of 3 months (range 3 weeks–6 months) and mean weight 5·6 kg (range 3–6 kg). Fifteen were breast fed and 14 had a history of parental smoking. None had a history of asthma in first degree relatives. Three of the children were receiving supplemental oxygen.

VARIABLES

Sao_2 was measured using a pulse oximeter (Nellcor N200E) with finger sensor attached to the patient and the output recorded on a chart recorder. Electrocardiogram leads were applied to check the heart rate and to detect arrhythmias. Heart rate, an electrocardiogram, and Sao_2 were monitored continuously on the chart recorder paper. Observations were noted of movement, crying, and coughing throughout the 110 minutes. In those receiving supplemental oxygen, oxygen was continued in the same inspired concentration as before the study.

PROTOCOL

Subjects were studied using a double blind, random allocation, crossover design. Continuous Sao_2 measurements were made over 110 minutes before and after nebulised salbutamol (2·5 mg/2 ml) or placebo (2 ml normal saline). Measurements were made during 30 minutes baseline, 10 minutes of first nebulisation, 30 minutes observation, 10 minutes of second nebulisation, and 30 minutes observation. Nebulisations were given using an Airlife jet nebuliser run from a compressed gas supply with a flow of 6 l/minute. For the three patients on oxygen, the concentration of oxygen was checked with an oxygen analyser (Teldyn), and maintained at the prestudy level using a Bird oxygen blender which could adjust the oxygen mixture and maintain a flow of 6 l/minute.

DATA ANALYSIS

The Sao_2 tracing was analysed using a digitising

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graphic tablet and a morphometric program on an Apple E computer. The average Sao_2 for each minute was determined from the graph using area under the curves for each minute. The mean Sao_2 for baseline was obtained over the first 30 minutes. The means of the 10 minute nebulisation period and mean of 5 minutes epochs after nebulisation for each patient were taken. Readings beyond 25 minutes after the second nebulisation could not be analysed due to interference from excessive movement in the majority of patients.

The results of the patients first given salbutamol or saline were analysed with a two way analysis of variance and the significance of change in desaturation from baseline determined with Dunnett's q test. The results of patients given salbutamol as the second nebulising solution were analysed with a one way repeated measure analysis of variance. No further statistical analysis was performed on patients receiving saline second as there was some persistent effect of salbutamol used as the first nebulising solution.

The periods of maximum desaturation from baseline, the times to reach maximum desaturation, and the times taken for recovery to baseline saturation for each group of patients were studied using a Kruskal-Wallis test. The differences betwen groups were analysed with χ^2 or Mann–Whitney non-parametric test where appropriate.

Results

For the 13 patients receiving salbutamol first there was a desaturation from mean baseline percent Sao_2 of 96·4 and 96·6 (during nebulisation) to 95·0, 95·0, 95·3, 95·4, and 95·4 at each five minute epoch after nebulisation (fig 1). A most significant decrease occurred five and 10 minutes after salbutamol nebulisation ($p<0·05$). After saline as the second nebulisation, there was no further desaturation with an Sao_2 of 96·1 during nebulisation to 96·2, 96·5, 96·4, and 96·8 after nebulisation.

The eight patients receiving saline first also showed desaturation from a baseline Sao_2 of 97·2 and 96·8 (during nebulisation) to 96·3, 97·6, 97·5, and 97·5 for each five minute epoch after nebulisation, a significant drop being recorded five minutes after saline nebulisation (fig 2). However, the drop in Sao_2 was again more noticeable after salbutamol given as the second nebulisation, with Sao_2 of 97·4 during nebulisation and levels of 97·0, 95·9, 95·6, and 95·9 for each five minute epoch after nebulisation. A significant drop was seen 10 and 15 minutes after nebulisation.

Eleven of the 13 patients given salbutamol first had a desaturation from baseline after salbutamol. All eight given salbutamol second desaturated after this nebulisation. The maximum fall in Sao_2 from baseline was greater in those who received salbutamol first and those who received salbutamol after saline than those who received saline first (fig 3). Although there was no significant difference between groups for the median maximum falls in Sao_2 after the first nebulisation, nine of 13 had a maximum fall in Sao_2 greater than 4% after salbutamol as the first nebulisation compared with two of eight after saline as the first nebulisation ($p<0·05$).

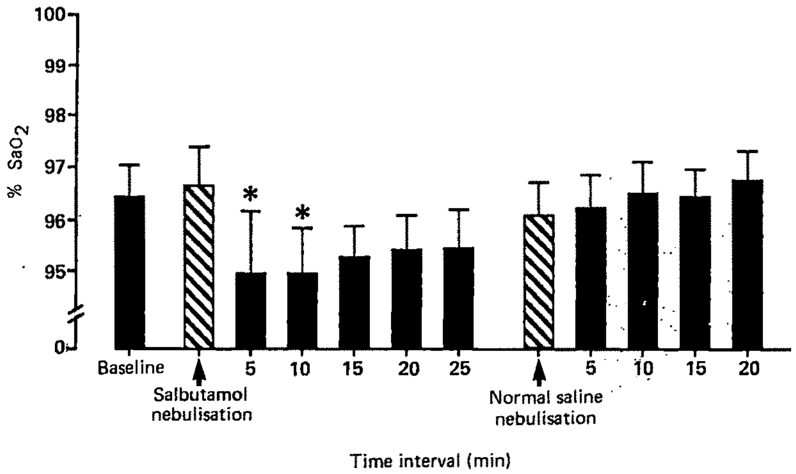

Figure 1 *Sao_2 after an initial salbutamol nebulisation with a saline nebulisation after 30 minutes; *significant decrease, $p<0·05$.*

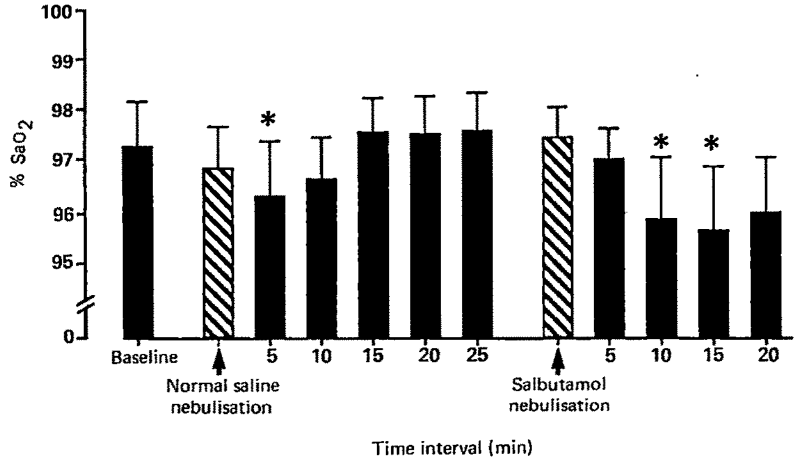

Figure 2 *Sao_2 after an initial saline nebulisation with a salbutamol nebulisation after 30 minutes; *significant decrease, $p<0·05$.*

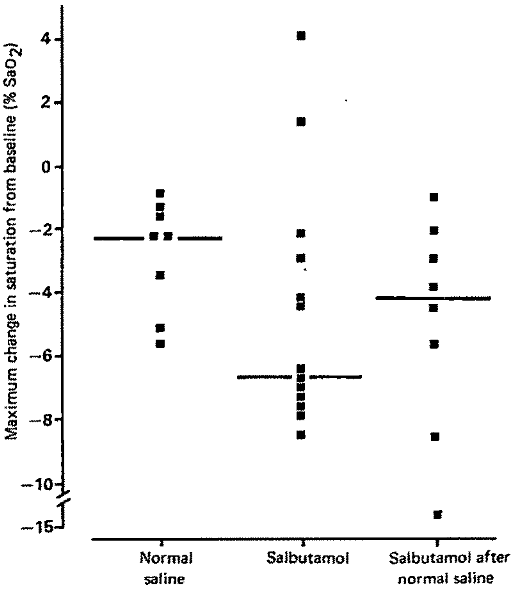

Figure 3 *Maximum change in Sao_2 after saline nebulisation, salbutamol nebulisation, and salbutamol nebulisation 30 minutes after a previous saline nebulisation. Medians shown.*

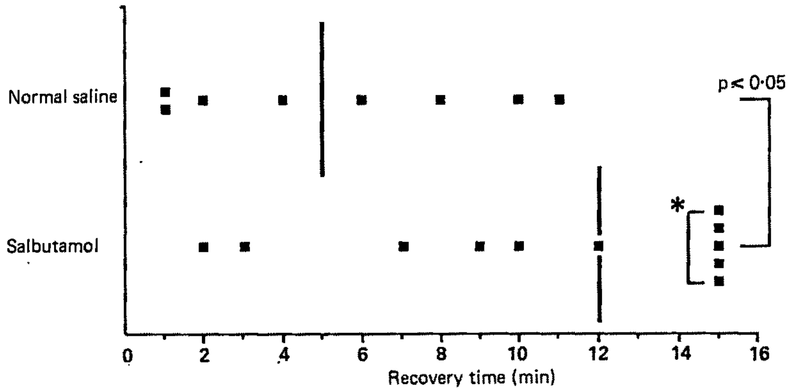

Figure 4 Time taken for $Sa{O_2}$ *to return to baseline after saline nebulisation and salbutamol nebulisation. *Denotes subjects where* $Sa{O_2}$ *had not returned to baseline before start of second nebulisation; they were allocated a recovery time of 15 minutes. Medians shown.*

Four of the eight who had salbutamol as the second nebulisation showed a maximum fall in $Sa{O_2}$ greater than 4%. Median time to reach maximal desaturation after the first nebulisation was not significantly different between the salbutamol and saline groups (9–10 minutes and five minutes respectively).

The 11 patients given salbutamol who desaturated took a median of 12 minutes to recover while the other eight patients given saline who desaturated took five minutes to recover (fig 4). The time required for patients given salbutamol to recover was significantly longer ($p<0{\cdot}05$).

Discussion

This study has demonstrated significant falls in $Sa{O_2}$ in infants with mild to moderate bronchiolitis given nebulisations of either salbutamol or saline with salbutamol having a more profound effect. Previous studies reporting the effect of bronchodilators in infants with bronchiolitis have used clinical scores or lung function measurements as outcome measures.[5 6 9 13–21] Most have shown no improvement and some reported deterioration in lung function after bronchodilator.[7 20 21] Soto *et al* found increased conductance in about 30% but the clinical significance was uncertain.[9] Reynolds measured arterial blood gas tensions but repeated measures could not be taken.[22] Some have argued that measurements used have not been appropriate to document the potential benefit that is sometimes clinically apparent. We reasoned that $Sa{O_2}$ is the clinically significant outcome measure of the adequacy of ventilation and perfusion in this condition and that oximetry is a useful non-invasive method to document the effect of bronchodilators on $Sa{O_2}$. We have therefore used oximetry to measure the response to nebulised salbutamol over 30 minutes.

The study was a randomised, double blind, crossover design where patients acted as their own control. Chloral hydrate has been used in previous studies.[7 8 13 14 21] As desaturation may occur with sedation in moderately sick infants with bronchiolitis no sedation was used in this study. Although some infants had coughing spells, they were not prolonged and did not limit measurements. We have also selected a group of infants aged under 6 months with proved respiratory syncytial viral infection and no previous wheezing or other illness to avoid confounding by case mix. There is considerable confusion about the diagnosis of asthma in this age group and its association with bronchiolitis.

In this study we have demonstrated that infants have significant desaturation when given salbutamol first or after saline nebulisation. Saline nebulisation also caused desaturation; however, the fall in $Sa{O_2}$ was greater and took longer to recover with salbutamol than with saline. The bronchodilator effect after salbutamol inhalation starts at 5–10 minutes and can last up to two to four hours.[25] The desaturation noted occurred at the time of maximal action of salbutamol and was consistent whether salbutamol was given first or second.

Desaturation was also seen with saline nebulisation, but the effect was smaller, and was more transient than for salbutamol. We assume that the desaturation with saline was related to disturbance of the baby. The mechanism of action of the salbutamol is unclear, but may be due to airway narrowing, vascular dilation leading to shunting, or both. The time course is different to that usually seen in adults with presumed shunting after salbutamol and we would suggest that the salbutamol aerosol also appears to impair ventilation in these infants by an irritant or osmotic effect of the aerosolised nebulising solution.[20]

Although the median fall in $Sa{O_2}$ was small, there were some infants who demonstrated a drop of 10% or more. These infants had mild disease at the time studied and this effect in an infant with severe disease could be significantly detrimental. Some previous studies have noted hypoxia[7] and deterioration in lung function[14 21] after bronchodilators in wheezy infants.

Nebulisations do not benefit infants with bronchiolitis who are already distressed. Salbutamol aggravates this process and cannot be recommended. In the event of an uncertain clinical diagnosis when assessment of a response to salbutamol is thought indicated, monitoring with pulse oximetry should be used.

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Birth weight and the health of nations

Professor Eva Alberman in her presidential address to the section of epidemiology and public health of the Royal Society of Medicine (*Journal of the Royal Society of Medicine* 1991;**84**:257–60) pointed to the value of birthweight statistics as a measure of the health status of a population.

Birth weight is the most powerful predictor of infant survival affecting both neonatal and postneonatal components of infant mortality. Usually the lowest infant mortality is found in babies whose birth weights are about 500 to 1000 g above the mode, although there is a slight increase in mortality at very high birth weights. It is suggested that the disparity between optimal and modal birth weight may be due to the birthweight curve being displaced to the left by the presence at the lower end of the distribution of babies with a pathological cause for their low weight but it is difficult to isolate 'normal' babies to define a pure 'normal' distribution.

Clearly there are biological factors which affect both birth weight and mortality. Girls tend to have a slightly lower birth weight and they have a lower infant mortality for all birth weights. Ethnic differences in birth weight and mortality are probably partly genetic but largely environmental. In the United States the modal birth weight for black babies is about 400 g less than for white. Below a birth weight of about 2000 g infant mortality is less in blacks presumably because small black babies are more 'normal' or more mature than small white babies. At birth weights above 3000 g infant mortality in blacks exceeds that in whites. The findings are similar in relation to maternal smoking: at low birth weights the babies of smoking mothers have a slightly lower mortality that those of non-smokers but babies of smoking mothers who weigh over 3000 g at birth have a higher first year mortality than those of the same birth weight whose mothers do not smoke.

In England and Wales the mean birth weight up to 1986 had changed little over the last 30 years being 3315 g in 1958, 3302 g in 1970, and 3318 g in 1986 but the percentage of babies weighing 3500 g or more at birth rose from 35·9% in 1983 to 38·6% in 1989. Since 1986 there appears to have been some increase in mean birth weight which has been most marked in the less privileged social classes.

A further decrease in maternal smoking and improved maternal health and nutrition among disadvantaged groups would probably lead to higher birth weights and lower infant mortality.

ARCHIVIST

Archives of Disease in Childhood 1991; **66**: 1065–1067

Ultrasonography to diagnose and exclude intussusception in Henoch-Schönlein purpura

S C Hu, M S Feeney, M McNicholas, D O'Halpin, R J Fitzgerald

Abstract

Abdominal pain is a frequent symptom in the child with Henoch-Schönlein purpura and raises the suspicion of intussusception or perforation. One hundred and fifty two children with a diagnosis of Henoch-Schönlein purpura over 11 years were reviewed. Of these 60 had abdominal pain, 19 gastrointestinal bleeding, and nine were suspected intussusception. Intussusception was confirmed in two of these cases with ultrasonography.

Ultrasound is an important tool in the early diagnosis of intussusception complicating Henoch-Schönlein purpura. Where the intussusception appears loose an expectant policy, with careful monitoring, may allow spontaneous reduction. It may also be used in monitoring patients for postoperative recurrence of intussusception, mural haematoma, and uncomplicated intestinal vasculitis with oedema.

Abdominal pain and gastrointestinal bleeding are common manifestations of Henoch-Schönlein purpura, resulting from vasculitis, intestinal oedema, mural haemorrhage, intussusception, necrosis, and perforation.[1–3]

Intussusception is an uncommon complication, yet its diagnosis is made more difficult in this situation.[4 5] Not only is its clinical presentation less distinctive, especially when the child already had abdominal symptoms and signs, but definitive diagnosis and treatment by barium or air enema is made more hazardous in view of the underlying intestinal vasculitis and may not be accessible by the enema as it will usually be in the small intestine.[6]

Ultrasonography was useful in the diagnosis of intussusception in two recent cases. To try to establish the extent of the problem it was decided to review the surgical experience in all patients admitted to the hospital with Henoch-Schönlein purpura over an 11 year period.

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Accepted 21 April 1991

Patients and methods

A chart review was made of patients admitted with the diagnosis of Henoch-Schönlein purpura from January 1980–December 1990 to determine the incidence of abdominal symptoms and surgical complications.

Results

Records of 152 patients were available for study, 60 of these experienced abdominal pain, 19 had gastrointestinal bleeding, and nine were suspected of having intussusception. Intussusception was excluded in most of the cases either by clinical examination, plain film of the abdomen, and more recently by ultrasound in five cases. It was confirmed in two cases by ultrasound, which constituted 1·3% of the patients analysed, and these are reported below.

CASE 1

A 5 year old boy was admitted in 1989 with a two day history of swelling of the feet and wrists, a purpuric rash on the ankles, scrotal erythema, vomiting, and intermittent abdominal pain. Urine analysis revealed proteinuria. A clinical diagnosis of Henoch-Schönlein purpura was made. His symptoms settled and he was discharged after six days.

One week later he was readmitted to the hospital with acute severe abdominal pain, tenderness all over the abdomen but no mass was palpable. A plain film of his abdomen was suggestive of intussusception, which was confirmed by ultrasound (fig 1). Hydrostatic or barometric reduction was not attempted in view of the underlying vasculitis. At laparotomy an ileoileal intussusception was identified and reduced manually with some difficulty. Though the bowel was congested looking it was viable with no perforation, and an appendicectomy was done.

Initially he had an uncomplicated recovery,

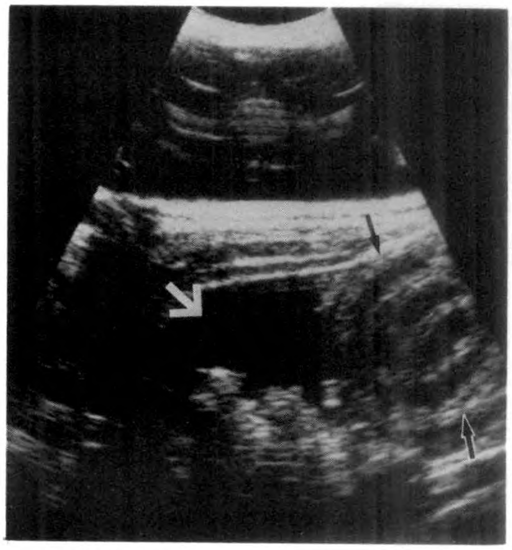

Figure 1 Ultrasound scan of a large intussusception with typical 'swiss roll' appearance (black arrows) and surrounding free fluid (white arrow).

but four days postoperatively he developed severe crampy abdominal pain. Abdominal ultrasound again demonstrated an intussusception in the right flank. At laparotomy on this occasion a caecocolic intussusception was reduced manually with little difficulty. A healthier looking small bowel was sutured side to side over a suspicious and slightly ischaemic looking patch at the site of the previous intussusception. The child recovered slowly and was discharged 18 days postoperatively.

Four days later he was readmitted with abdominal pain and bloodstained faeces. Abdominal ultrasound demonstrated thickened loops of bowel but no evidence of intussusception. He was treated conservatively. His renal involvement was treated with steroids. He eventually settled and was discharged home.

CASE 2

A 9 year old boy was admitted in 1990 with a seven day history of pain and swelling of his ankles and wrists, purpuric rash over both his legs and buttocks, and colicky abdominal pain. Two days after his admission, when his abdominal pain became more severe, an ultrasound was done which revealed an intussusception in the right flank, which the radiologist visualised to be occurring and reducing, and concluded to be 'loose' (fig 2). It was decided to observe him overnight with the expectation that it might reduce spontaneously, and to repeat the abdominal ultrasound in the morning. This revealed that the intussusception was no longer present. His abdominal symptoms improved.

Three days later he again started to complain of intermittent colicky abdominal pain. A plain film of his abdomen revealed absence of caecal gas shadow. The abdominal ultrasound confirmed an intussusception, which on this second occasion appeared tight. A laparotomy was carried out without delay and an ileoileal intussusception was easily reduced manually, with plication of the mesentry of the terminal ileum to prevent recurrence, and an appendicectomy was done. He gradually improved and on recovery was discharged home.

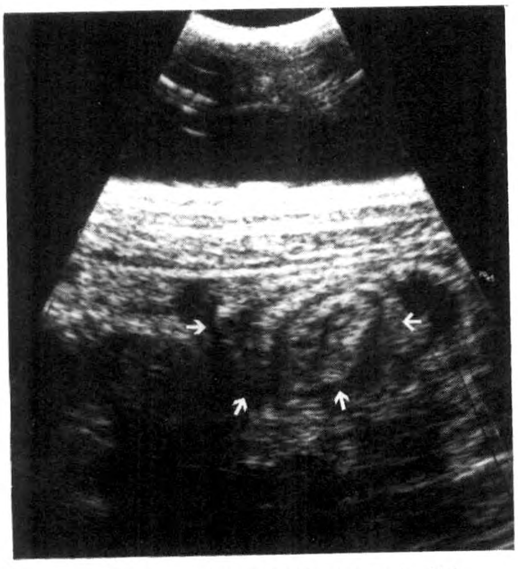

Figure 2 Small loose intussusception (arrows) which reduced spontaneously.

Discussion

Some authors have drawn attention to the difficulty in the diagnosis of intussusception in Henoch-Schönlein purpura.[4 5 7] Identification of patients with this complication may be obscured for a number of reasons:

(1) Abdominal symptoms are frequent among patients with Henoch-Schönlein purpura who do not have intussusception.

(2) The presentation of intussusception is variable and may be identical to that of intestinal vasculitis and oedema, or mural haematoma, not requiring surgery.[2 3 5]

(3) Intussusception may occur at any stage of the illness.[2 5]

(4) After surgery intussusception may occur at a different site as seen in our first case.

(5) The place of contrast studies is limited by its invasiveness, and by the fact that most intussusceptions in Henoch-Schönlein purpura are in the small bowel.[6] Especially in the presence of vasculitis with severe intestinal involvement, there may be a high risk of perforation.

A previous report has described the use of ultrasound in the diagnosis of a case of intussusception in Henoch-Schönlein purpura.[6] Our report highlights the use of ultrasound to diagnose or exclude intussusception as a complication of Henoch-Schönlein purpura. It is also useful as an efficient, non-invasive, and repeatable method in the postoperative period to identify or exclude recurrence or further intussusception. It may provide a way of carefully monitoring cases in which the intussusception is loose and may reduce spontaneously.

Our study confirms that abdominal symptoms are present in a significant number of children with Henoch-Schönlein purpura. Perforation of bowel is easily diagnosed on a plain film of the abdomen and was not seen in our group of patients. Intussusception was seen, but the incidence was lower than that reported in other series.[1 3]

A total of 60 patients spread fairly evenly throughout the 11 year review had abdominal pain, but six of the nine suspected cases of intussusception occurred in the last two years. It is possible that intussusception in Henoch-Schönlein purpura is a more common occurrence than we have found, and that the intussusception may be loose and may reduce spontaneously as was shown by ultrasonography in our case 2. When a second intussusception occurred in this case, it was described as tight and therefore laparotomy was carried out immediately.

The intussusception was reduced easily and it is possible that it would have reduced had an expectant policy been followed. Despite this, in our current state of knowledge, we would have to recommend that the surgical line be followed when the ultrasound picture is suggestive of a tight intussusception. However, it would seem reasonable to follow a 'wait and observe' policy if it appears loose with serial ultrasonography.

We would not consider attempting a therapeutic air enema reduction (or any other contrast enema) as the bowel is generally inflamed, haemorrhagic, and oedematous as a result of the vasculitis, making perforation a significant risk, and also as the intussusception is usually in the small bowel and will not be accessible by this form of treatment.[6]

Patients in whom laparotomy has been avoided by the use of ultrasound can also be usefully monitored by serial ultrasound examination to assess the resolution of free fluid, intestinal oedema, and mural haematoma. Careful clinical monitoring is essential in patients with Henoch-Schönlein purpura with prominent abdominal symptoms, complemented when necessary by serial ultrasound examinations. Not only can the clinician thus identify the complication of intussusception at an early stage, but also needless laparotomy may be avoided in patients with uncomplicated intestinal vasculitis and oedema.

We thank Mr P Puri for kindly granting his permission to present case 2 in this article. We also thank the staff in the medical records department, the Children's Hospital, Temple Street, for making possible the production of this article.

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Enzyme replacement in Gaucher's disease

Gaucher's disease is due to a deficiency of the enzyme glucocerebrosidase in macrophage lysosomes. Giving placental glucocerebrosidase intravenously gave poor results probably because the enzyme was taken up by hepatocytes which do not accumulate glucocerebroside in this disease. For more success, so the theory goes, the enzyme must be delivered to the affected macrophages. That can be done by taking advantage of the special properties of macrophage plasma membranes. American workers have prepared macrophage-targeted glucocerebrosidase by sequential deglycosylation of the oligosaccharide chains of the enzyme and a recent report in the *New England Journal of Medicine* (Norman W Barton and colleagues, 1991;**324**:1464–70) describes the effects of its administration to eight children and four adults with non-neuronopathic Gaucher's disease.

The enzyme was given by intravenous infusion every two weeks for nine to 12 months. There were no apparent adverse effects. A significant reduction in spleen size occurred in all 12 patients with an accompanying rise in haemoglobin concentration. Serum acid phosphatase activity fell in 10 patients and liver volume in five. Plasma glucocerebroside concentrations fell in nine patients. The changes occurred slowly over six to nine months or more. Bone pain improved and three patients showed improvement in long bone *x* ray changes though the skeletal effects were even slower than the visceral or haematological. All the patients reported increased wellbeing, more enthusiasm for daily activities, and reduced fatigue.

Clearly these results are extremely encouraging. The authors comment that the same approach may benefit people with other metabolic diseases. Is this the dawn of a new era of targeted enzyme therapy or is it a false dawn? Keep your fingers crossed.

ARCHIVIST

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Outcome of confirmed symptomatic congenital cytomegalovirus infection

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Abstract

Sixty five neonates with confirmed symptomatic congenital cytomegalovirus infection were followed up prospectively until they were 3 to 4 year of age. Twenty nine children (45%) had neurological impairment of whom 22 had gross motor or psychomotor abnormalities; in the remaining seven sensorineural deafness was the main abnormality. Infants who had had neurological signs during the neonatal period had a worse prognosis than those who had not, with 16/22 (73%) and 13/43 (30%) having neurological deficit at follow up, respectively. Our results indicate that the prognosis for infants with symptomatic congenital cytomegalovirus infection is better than previously reported.

Cytomegalovirus is the most common cause of congenital infection with an incidence in the United Kingdom of 3/1000 live births.[1] Over 90% of children with congenital cytomegalovirus infection have no symptoms at birth and in most there are no adverse effects.[1] There is insufficient information on outcome in the small proportion of infected infants who present with cytomegalovirus related symptoms at birth. In this paper we describe the outcome in 65 children with symptomatic congenital cytomegalovirus infection and relate prognosis to specific neonatal presentation.

Patients and methods

Infants with congenital cytomegalovirus infection were identified through reports from laboratories in England and Wales to the Communicable Disease Surveillance Centre (CDSC) between January 1983 and May 1987. The paediatrician in charge was identified through the reporting microbiologist, and sent a detailed questionnaire about the child's clinical condition during the neonatal period and at the time of the last consultation. After two years, a follow up questionnaire was sent to the same clinician or, if hospital care had been discontinued, to the general practitioner. Only infants meeting the following criteria were included. (1) Isolation of cytomegalovirus or detection of specific IgM before 21 days of age (as acquired cytomegalovirus infection is common in early life,[2] children with infections diagnosed beyond this age were not included). (2) Presence of signs consistent with congenital cytomegalovirus infection in the first four weeks of life (infants in whom the only signs were low birth weight, prematurity, or jaundice were not included). (3) Survival beyond the age of 4 weeks.

Results

During the study period, 142 reports of cytomegalovirus infection in children under the age of 1 month were received from collaborating laboratories. Further information was obtained on 125 of these (88%) and permitted exclusion of 19 infants in whom the diagnosis was confirmed between 21 and 28 days of age, 31 asymptomatic infants and eight infants who died in the neonatal period. Of the 67 infants who met the study criteria, two were lost to follow up, and 65 were followed up to a median age of 3·5 years (range 1·0–6·4).

NEONATAL SIGNS AND SYMPTOMS

Hepatomegaly, splenomegaly, or purpura were reported either alone or in combination in 48/65 of infants (74%). Neurological signs (other than microcephaly) were less common, and were reported in 22 infants (34%). These included fits (n=8), cerebral calcification (n=5), and abnormal tone, abnormal movements, or irritability (n=16). Thirteen infants (20%) had respiratory problems, which ranged from tachypnoea to the need for ventilation. Most infants had retarded growth or microcephaly, 36 (55%) had a birth weight below the third centile, and 26 (40%) had a head circumference below the third centile for gestation.[3]

CONDITION AT FOLLOW UP

At follow up 36/65 children (55%) were reported to be normal or to have only a minor abnormality. The latter included two children with mild hypotonia and ataxia, three with conductive hearing loss, and one with both of these problems. There were 29 children (45%) with definite neurological impairment. In seven (11%) the principal deficit was sensorineural deafness (bilateral, n=6 and unilateral, n=1) and three of them also had mild ataxia or awkward gait. The remaining 22 children (34%), one of whom died aged 2 years, had gross motor or psychomotor problems. These included spastic quadriplegia (n=9), diplegia or hemiplegia (n=4), dyskinetic cerebral palsy (n=1), and severe global psychomotor retardation (n=6). The remaining two children had problems not normally attributed to cytomegalovirus infection—one had bilateral arthrogryphosis of the lower limb joints and one a congenital myopathy. Of these 22 children, 15 were microcephalic at follow up, and although full auditory or visual assessment was not always made, associated sensorineural hearing loss was reported in eight, chorioretinitis in three, and cortical blindness in four.

Outcome by neonatal presentation. Results are numbers (%)

Neonatal presentation	*No of infants*	*Condition at follow up*		
		Normal	*Definite handicap*	
			Motor or psychomotor problems	*Sensorineural deafness*
Group 1*	22	6 (27)	14 (64)	2 (9)
Group 2†	35	22 (63)	8 (23)	5¶ (14)
Group 3§	8	8 (100)	0	0
All groups	65	36 (55)	22 (34)	7 (11)

*Infants with neurological signs.
†Infants with hepatomegaly, splenomegaly, or purpura but no neurological signs.
§Infants not included in groups 1 or 2.
¶One unilateral.

OUTCOME IN RELATION TO NEONATAL PRESENTATION

The children were divided into three groups according to neonatal presentation. Those in group 1 presented with abnormal neurological signs (other than microcephaly). Children in group 2 presented with hepatomegaly, splenomegaly, or purpura (either alone or in combination) but had no early neurological signs. Children in group 3 were those not included in groups 1 and 2 who presented with either microcephaly, respiratory problems, or both. At follow up the children in group 1 were at highest risk, and those in group 3 at lowest risk, of subsequent neurological deficit (table).

Of the 26 children who had microcephaly at birth, 16 were still microcephalic and six had a head circumference above the third centile at follow up (in four children the head circumference had not been measured).

Discussion

This is the largest prospective study of the outcome of symptomatic congenital cytomegalovirus infection so far reported to our knowledge. The aim was to determine the incidence of neurological deficits in children who presented with symptomatic infection in the neonatal period and to relate outcome to neonatal signs and symptoms. The minimum incubation period of acquired infection is 21 days and the study was restricted to infections confirmed before this age. Acquired infection in early life is common,[2] and where cytomegalovirus is isolated from children after 21 days of age neurological impairment may be wrongly attributed to congenital infection.

The neonatal signs and symptoms of congenital cytomegalovirus infection found in this study were of similar type and incidence to those previously described.[4–6] The most common presentations were hepatomegaly, splenomegaly, or purpura which were seen in 48/65 infants (74%). It was reassuring that 36 children (55%) were normal at follow up. Neurological signs in the neonatal period, however, were associated with a poor prognosis, and 16 of those 22 children (73%) had serious subsequent deficits.

The overall prognosis for the children in our study was better than that reported from the United States.[4] As this earlier study was based on referrals to a specialist hospital, however, it may have included children with more severe neonatal signs. Our study confirms the observations of three smaller studies in which children who had central nervous system involvement during the first year of life had a poor outcome.[7–9] There have been conflicting reports of the outcome in infants in whom microcephaly was present at birth.[7 10] We found that the prognosis for children presenting with either microcephaly or respiratory problems alone was relatively good, and probably similar to that for children who are symptom free during the neonatal period.[11 12]

In conclusion, the findings of this study will permit a more accurate prediction of the outcome of symptomatic congenital cytomegalovirus infections and provide a basis for more confident counselling of parents by paediatricians. As only 19 of the 65 children were over 4 years of age at their last review, continued follow up of this group is planned to detect the possible occurrence of later abnormalities.

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Partial splenectomy in sickle cell syndromes

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Abstract

Partial splenectomy was carried out in four children with homozygous sickle cell disease and eight children with sickle cell β thalassaemia. It was performed in order to preserve splenic contribution to the host defence against infections while suppressing hypersplenism or the risk of recurrence of acute splenic sequestration. Indications for this surgical operation were acute splenic sequestration (n=1), hypersplenism (n=5), and acute splenic sequestration and hypersplenism (n=6). Surgery was uneventful in 11 patients. A significant reduction of blood requirements and a significant decrease of the number of hospitalisations/patient/year were observed after splenectomy. No recurrence of hypersplenism or acute splenic sequestration occurred and no severe infection was noticed during the follow up period after surgery (mean (SD) 4·2 (2·8) years; range 6 months–7 years). Mean haemoglobin concentration and leucocyte and platelet counts increased after surgery. The benefit of partial splenectomy compared with total splenectomy to treat acute splenic sequestration or hypersplenism in sickle cell disease is discussed.

There are several severe splenic complications that may occur in children with sickle cell disease: not only hyposplenism, which is a common event in this disease, but also acute splenic sequestration and hypersplenism. Acute splenic sequestration is defined as a fall in the haemoglobin concentration of more than 20 g/l, with evidence of marrow compensation (increased number of reticulocytes or normoblasts), and an acutely enlarged spleen.[1] Acute splenic sequestration is a major cause of mortality and morbidity in children with sickle cell disease younger than 5 years.[2] Death may occur during the first attack or during a recurrence.

A definition of hypersplenism includes: (i) a chronically enlarged spleen more than 4 cm below the left costal margin; (ii) a haemoglobin concentration less than 65 g/l; (iii) more than 15% reticulocytes; and (iv) a platelet count less than 200×10^9/l. These variables must have been found on at least two occasions.[1] Hypersplenism makes patients dependent on regular blood supplies, with repeated hospitalisations, and therefore exposes them to transfusional risks. Many authors thus recommend splenectomy in children with acute splenic sequestration or hypersplenism despite risks of infection caused by splenectomy. In order to preserve splenic contribution to the host defense against infections, while suppressing hypersplenism or the risk of recurrence of acute splenic sequestration, we have performed partial splenectomy in 12 children affected with major sickle cell syndromes. We report here our experience of the haematological and infectious consequences of this surgical technique.

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Patients and methods

Twelve patients affected with major sickle cell syndromes were included in the study. There were four children with homozygous sickle cell disease and eight with sickle cell β thalassaemia. Mean (SD) age at the time of the surgical operation was: 7 (3) years (range 3–11 years). Indications for partial splenectomy for patients with homozygous sickle cell disease were: acute splenic sequestration (n=1), hypersplenism (n=2), and hypersplenism plus one episode of acute splenic sequestration (n=1). In patients with sickle cell β thalassaemia indications were: hypersplenism (n=3) and hypersplenism plus one episode of acute splenic sequestration (n=5).

SURGICAL TECHNIQUE

Partial splenectomy was performed according to a previously described technique.[3]

HAEMATOLOGICAL DATA

Blood supplies (expressed in litres of blood received per year) and the number of hospitalisations per year for each patient were determined the year before splenectomy and during the follow up period. Mean haemoglobin concentration and leucocyte and platelet counts were studied in the same periods. Mean values correspond to two to five determinations according to the patients.

SPLENIC HOST DEFENCE AGAINST INFECTIONS

Spleen host defence against infections was discerned by (i) clinical survey, (ii) residual splenic mass measurement evaluated by scintigraphy or echography, and (iii) variations of serum IgM concentrations. All patients were immunised before splenectomy with a polyvalent pneumococcal vaccine. A systematic prophylactic treatment with penicillin was pursued after surgery as is usual for every child with sickle cell disease.

The follow up after splenectomy was at 4·2 (2·8) years (range 6 months–7 years).

Table 1 Clinical results in 12 patients with major sickle cell syndromes having partial splenectomy

	Year before partial splenectomy		*Follow up period*	
	Homozygous sickle cell disease (n=4)	*Sickle cell β thalassaemia (n=8)*	*Homozygous sickle cell disease (n=4)*	*Sickle cell β thalassaemia (n=8)*
Mean (SD) blood supplies (l/year)	2·1 (0·3)	4·2 (1·5)	0·62 (0·70)	0·21 (0·25)
Mean (SD) No of hospitalisations	4·7 (5)	2·4 (3·2)	1·5 (1·3)	0·37 (0·7)

Table 2 Results of laboratory investigations in 12 patients with major sickle cell syndromes having partial splenectomy

	Year before partial splenectomy	*Follow up period*	*Significance (p value)*
Mean (SD) annual haemoglobin concentration (g/l)	50 (5)	83 (8)	<0·001
Mean (SD) leucocyte count ($\times 10^9$/l)	9 (3)	13 (3·8)	<0·001
Mean (SD) platelet count ($\times 10^9$/l)	134 (40)	522 (100)	<0·001
Mean (SD) IgM concentration (g/l)	16 (8)	15 (8)	NS

NS: not significant.

Results

Surgery was uneventful in 11 patients. A bilateral pneumonia occurred in one patient on the third postoperative day. Bacteriological investigations were negative and the patient promptly recovered with antibiotic treatment.

A reduction of blood requirements and a decrease of the number of hospitalisations/patient/year was observed after splenectomy (table 1). No recurrence of hypersplenism or acute splenic sequestration occurred.

Mean haemoglobin concentrations and leucocyte and platelet counts before and after surgery are shown in table 2 (the data for both groups of patients were combined because they do not differ significantly). All three of these variables were significantly increased after splenectomy (p<0·001). Platelet count immediately after surgery was 540 (273)$\times 10^9$/l. No thrombosis occurred and platelets returned to normal in all patients within one year.

No severe infection was observed during the follow up period.

Mean residual splenic size was 4·6 (0·7) cm in six patients according to scintigraphic data and 4·6 (1·7) in seven others according to the echographic data; mean splenic size before surgery was 13 (2·7) cm. Mean IgM concentrations did not differ before and after splenectomy (16 (8) and 15 (8) g/l respectively).

Discussion

The underlying mechanisms leading some sickle cell children to have an hypertrophic spleen, responsible for red blood cell sequestration and destruction, instead of an atrophic unfunctional spleen usually observed in this disease, are not known.

Splenic sequestration may occur in all major sickle cell syndromes: homozygous sickle cell disease, sickle cell haemoglobin C disease, and sickle cell β thalassaemia. Our series included twice as many children with sickle cell β thalassaemia than with homozygous sickle cell disease; this is in agreement with the higher prevalence of splenomegaly in the former. Hypersplenism and acute splenic sequestration could be the chronic and acute expressions of the same process. It has already been shown that hypersplenism was much more common in patients with a history of acute splenic sequestration than in others (p<0·001).[4] It is also possible that episodes of acute splenic sequestration may be found with hypersplenism,[4] as it occurred in six out of 12 of our patients.

A prospective study of a cohort of Jamaican children with sickle cell disease who had been followed up from birth indicates a prevalence of acute splenic sequestration in a 10 year period of 8·2/100 patient years of observation.[5] The first attack can occur from 3 months to 6 years of age. Recurrences may happen in about half the cases, and the overall case fatality rate is 9·8/100 attacks, concerning mostly the children under 2 years.

Two methods of treatment have been proposed for children surviving their first attack of acute splenic sequestration: a short term transfusion programme and splenectomy. A recent study has shown that blood transfusion did not prevent recurrent sequestration as four out of 12 patients who were transfused experienced a new attack on treatment.[6] Furthermore, the risk of recurrent sequestration is highest soon after the transfusion programme is discontinued. Regular blood supplies expose children to viral contamination, alloimmunisation, and iron overload. Thus splenectomy seems the appropriate treatment for children having experienced acute splenic sequestration or exposed to the same complications on account of their hypersplenism. This intervention is nevertheless to be avoided in very young infants because of the immunological impairment it induces. The spleen has a major role in phagocytosis for blood borne antigens in the presence of low concentration of antibodies,[7] it synthesises specific IgM antibodies and opsonins such as tuftsin and properdin,[8] and intervenes in the alternative complement pathway.[9] This anti-infectious role of the spleen remains important in chidren with sickle cell disease since severe infections have been reported in a cohort of 60 children with sickle cell disease who underwent splenectomy: two deaths resulting from sepsis after splenectomy and 17 acute chest infections occurred, mainly in children under 2 years.[1] Partial splenectomy could be thus a possible alternative as it reduces splenic hypertrophy while preserving some immunological function of this organ. The ability of partial splenectomy to reduce hypersplenism has already been shown in thalassaemic patients.[10] It is clearly shown in our series of patients with sickle cell disease as we found significantly higher concentrations of haemoglobin and lower blood requirements with a follow up of more than five years in eight cases. No recurrence of acute splenic sequestration or hypersplenism occurred, there was no severe infection, and the IgM concentrations remained stable after the intervention. Although only a few patients were involved, we conclude that partial splenectomy can be of benefit in treating acute splenic sequestration or hypersplenism in children with sickle cell disease. A rigorous follow up must be maintained to observe the long term consequences of this intervention.

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Focal nodular hyperplasia of the liver: a link with sickle cell disease?

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Abstract

Focal nodular hyperplasia is a benign liver tumour that is rare in children. We report the second case of a child with sickle cell disease presenting with symptomatic focal nodular hyperplasia. The possible pathogenesis of focal nodular hyperplasia and the association with sickle cell disease are discussed.

Focal nodular hyperplasia of the liver is a rare benign lesion found predominantly in women during their reproductive years.[1] It consists of a well circumscribed area of hyperplastic liver parenchyma that may contain a stellate fibrous scar. The lesion is usually asymptomatic and is an incidental finding. We describe a patient with sickle cell disease presenting with a symptomatic lesion of focal nodular hyperplasia. This is the second description of such an association[2] and we discuss whether sickle cell disease is a pathogenetic mechanism for the development of focal nodular hyperplasia.

Case report

A 6 year old West Indian girl with homozygous SS sickle cell disease presented with abdominal pain, headache, and night sweats. She had been admitted one year previously with a chest infection and sickle crisis. She was taking prophylactic antibiotics. Apart from sickle cell disease there was no other significant medical or family history.

On examination she appeared anaemic but was not jaundiced. A firm non-tender mass was palpable in the epigastrium. The results of biochemical investigations were haemoglobin concentration 72 g/l, white cell count $8{\cdot}1\times10^9$/l, platelet count 213×10^9/l, albumin 38 g/l, bilirubin 30 μmol/l, and activities of alkaline phosphatase 201 IU/l, aspartate transaminase 111 IU/l, and γ-glutamyltransferase 146 IU/l. A test for serum α fetoprotein was negative. An ultrasound scan showed a 6 cm well defined mass in the left lobe of the liver. The lesion had a similar density to normal liver on computed tomography (fig 1) and was shown to be avascular on hepatic angiography (fig 2).

At operation, after exchange transfusion, the solid mass was found to be restricted to segments 2 and 3 of the left lobe and was resected. She was discharged home on the ninth postoperative day.

The cut surface of the tumour was smooth with focal areas of haemorrhage, but there was no stellate scar. The microscopic appearance of fibrous bands transecting liver tissue with expanding portal tracts that contained dilated vascular channels and numerous bile ductules was typical of focal nodular hyperplasia (fig 3).

Discussion

Focal nodular hyperplasia is a rare benign liver tumour with fewer than 20% of cases presenting in children.[3] The majority are asymptomatic and usually arise on the surface of the liver beneath the capsule. Their aetiology is unknown, although an association with oral contraceptives has been reported.[4]

The radiological diagnosis depends on identification by ultrasound or computed tomography of a central scar. Angiographic findings of a hypervascular spoke wheel pattern of feeding

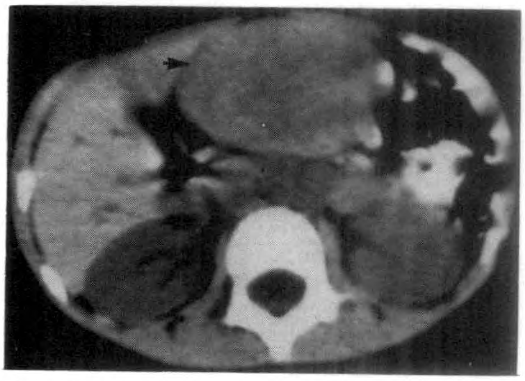

Figure 1 Computed tomogram without contrast showing the mass in the left lobe of the liver (arrow).

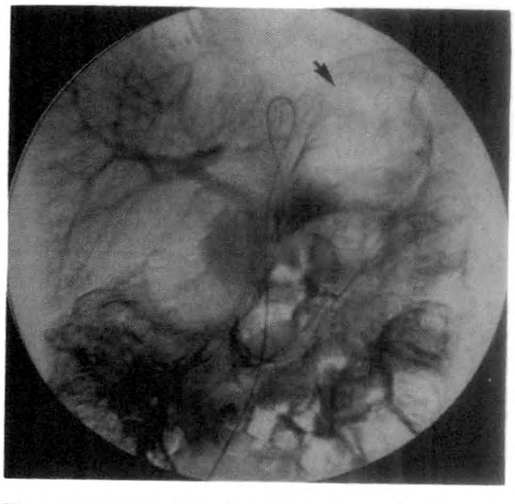

Figure 2 Venous phase of an hepatic digital subtraction angiogram showing an avascular mass in the left lobe of the liver (arrow).

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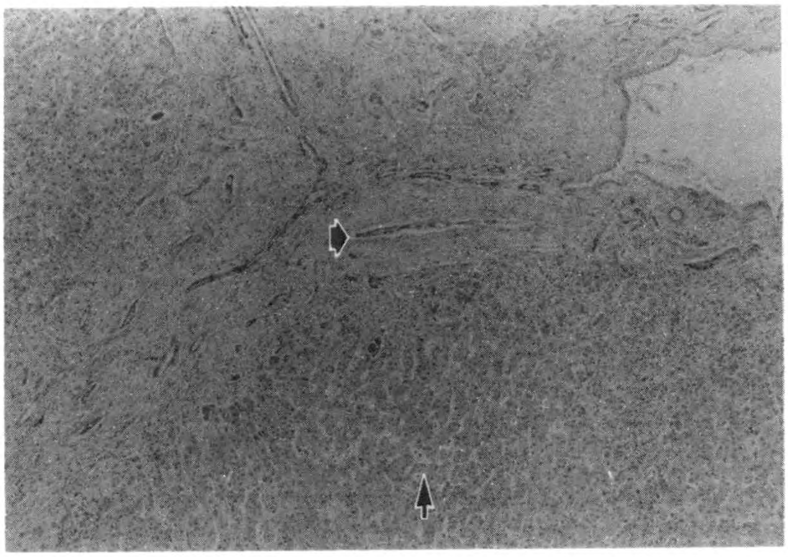

Figure 3 Section showing regenerative nodules of liver parenchyma (thin arrow) transected by fibrous bands with expanded portal tracts (thick arrow) containing dilated vascular channels and bile ductules (magnification × 100).

vessels which produce a dense capillary blush are diagnostic but uncommon.[5]

The management of asymptomatic lesions should be to confirm the diagnosis of focal nodular hyperplasia by liver biopsy, excluding benign lesions such as hepatic adenoma, mesenchymal hamartoma, or haemangioma and malignant lesions such as fibrolamellar carcinoma. Ultrasound follow up has been suggested. Symptoms may settle by withdrawal of oral contraceptives, but in other patients symptomatic lesions should be resected or if this is not possible they can be embolised.[1]

The pathogenesis of focal nodular hyperplasia has been considered to be neoplastic, hamartomatous, or a response to ischaemia or other focal injury. It has been suggested that the lesions arise as a hyperplastic response of liver parenchyma to differential blood flow caused by a pre-existing arterial malformation.[6] Poorly perfused areas undergo atrophy and well perfused areas develop regenerative nodules. Whelan *et al* suggested that increased blood flow and turbulence caused platelet disruption with thrombosis of smaller arterial vessels that lead to a release of platelet derived growth factor which may stimulate hepatocellular hyperplasia.[7] Oral contraceptives may affect the hepatic vasculature and influence the development of focal nodular hyperplasia.[4] Patients taking oral contraceptives tend to have larger, symptomatic lesions sometimes associated with haemangiomata.[1 8]

Occlusive lesions in small arteries and veins may also cause ischaemia followed by atrophy and regenerative nodules. In sickle cell disease blockage of small vessels by deformed red blood cells leads to tissue damage. Sequestration of sickled cells also lead to infarction. The resulting ischaemia and necrosis may provide an explanation for the development of focal nodular hyperplasia. Markowitz *et al* suggested that the primary abnormality may still be an underlying vascular anomaly and that ischaemia from sickle cell thrombosis acts as a stimulant to the development of focal nodular hyperplasia.[2]

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Oxygen saturation in cystic fibrosis

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Abstract

The availability of non-invasive oxygen saturation (Sa_{O_2}) measurement could prove to be a useful tool for following up the progress of patients with cystic fibrosis. The present study was undertaken to compare its use with other routine measurements in the clinic. A total of 100 patients with cystic fibrosis were compared with 50 patients with stable asthma. The children were aged between 5 and 16 years and were studied as outpatients. A positive correlation was found between forced expiratory volume in one second and Sa_{O_2} in the group with cystic fibrosis and in the comparison group. Median Sa_{O_2} in those with cystic fibrosis (94·0%) was significantly lower than in controls (97·0%). Significant correlations were also found in the patients with cystic fibrosis for the following: Shwachman-Kulczycki score, higher weight centiles, and chronic pseudomonas lung infection with or without staphylococci. An inverse correlation was found with the Chrispin-Norman chest *x* ray score. Sa_{O_2} measurements are useful in the outpatient assessment of patients with cystic fibrosis and compare well with other standard tests of disease severity.

Pulse oximetry is a reliable and simple method for assessing oxygen status in children at all ages.[1] It is non-invasive, easy to apply, and provides rapid results. The aim of this study was to assess oxygen saturation (Sa_{O_2}) in children with cystic fibrosis and to relate this to the patient's general condition and other specific measurements of clinical status.

Patients and methods

One hundred children with cystic fibrosis consecutively attending the outpatient clinic and 50 comparison patients with asthma, which was well controlled on routine medication, were included in this study over a six month period. They were aged between 5 and 16 years.

Sa_{O_2} was measured using an Ohmeda Biox 3700 pulse oximeter with a paediatric finger probe before the other lung function measurements. The saturation measurements were made after allowing the readings to stabilise; this usually took two to three minutes with a minimum time of 30 seconds. Lung function was assessed using a Vitalograph Compact spirometer to measure forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), peak expiratory flow rate (PEFR), and forced expiratory flow at 75% of expired FVC ($FEF_{75\%}$).

The clinical evaluation of the patients with cystic fibrosis was based on the Shwachman-Kulczycki score[2] utilising general activity, physical examination, nutrition, and findings on radiography (scoring system of 0–100; 100=excellent, <40=severe disease). Radiological assessment was undertaken blind by a physician experienced in cystic fibrosis (RD) and used the Chrispin-Norman score.[3] Chronic lung infection was considered to be the presence of the same pathogen in three successive sputum cultures over a six month period.

The lung function test results were expressed as percentage of predicted normal for height using reference values from the Brompton Hospital study, 1985 (unpublished observations). These values were obtained on 788 normal local schoolchildren of the same age, height, and sex distribution as those in our study. These data are most representative of the local population and compare well with standard reference values.[4] Weight was expressed as age centile for sex based on data obtained on normal children. Statistical analysis was by Pearson correlation and Wilcoxon rank sum test.

Results

One hundred patients with cystic fibrosis and 50 patients with stable asthma as a comparison group were studied. Thirty seven cystic fibrosis patients were aged less than 8 years, 40 were aged 8–12, and 23 were aged 12–16. The comparison group comprised 12 children aged less than 8 years, 23 aged between 8 and 12 years, and 15 aged between 12 and 16. There was a positive correlation between Sa_{O_2} and FEV_1 in the cystic fibrosis patients ($r=0{\cdot}5$, $p<0{\cdot}001$) (figure) and in the comparison group ($r=0{\cdot}4$, $p<0{\cdot}01$ by Pearson correlation); these data were normally distributed. The median values for Sa_{O_2} were: comparison group 97·0% (range=94–99%) and cystic fibrosis patients 94·0% (range=70–99%, $p<0{\cdot}001$). There was a significant correlation for patients with cystic fibrosis between Sa_{O_2} and clinical evaluation using the Shwachman-Kulczycki score ($p<0{\cdot}01$). There was an inverse correlation between Sa_{O_2} and Chrispin-Norman score ($p<0{\cdot}05$).

The median Sa_{O_2} difference between patients with cystic fibrosis with and without chronic lung infection was assessed using the Wilcoxon rank sum test. Cystic fibrosis patients with chronic pseudomonas infection (n=37) had a median Sa_{O_2} of 92·0% (range=75–97%) and without infection (n=6) 95·5% (range=94–97%;

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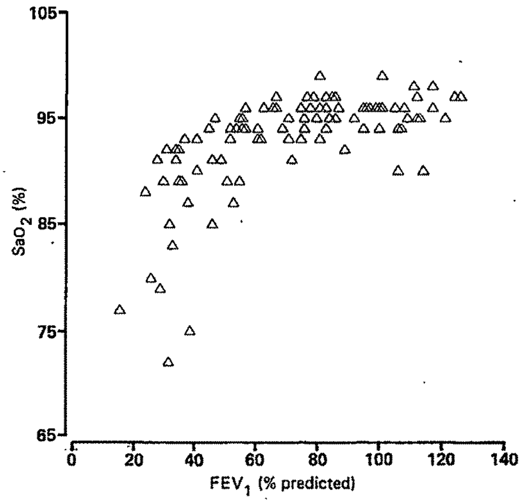

Oyxgen saturation (Sao$_2$) and forced expiratory volume in one second (FEV$_1$) % predicted for height in 100 patients with cystic fibrosis (includes seven overlapping points). Reproduced with permission from the Journal of the Royal Society of Medicine Supplement 1991;84(18):36–9, figure 1. Cystic fibrosis: yesterday, today and tomorrow by R Dinwiddie.

$p<0{\cdot}01$). Those with chronic pseudomonas and staphylococcal lung infection combined (n=6) had a median Sao$_2$ of 93% (range=79–96%; $p<0{\cdot}01$). Patients with chronic staphylococcal lung infection only (n=34) showed a higher Sao$_2$ (median 95·0%, range=87–99%) than those with pseudomonas only (median 92·0%; $p<0{\cdot}001$). The higher weight centiles (>50th) correlated well with higher Sao$_2$ values (>94%) for cystic fibrosis patients ($p<0{\cdot}01$).

Discussion

There was a positive correlation between the Sao$_2$ and % predicted FEV$_1$ in each patient (figure); this was not unexpected. In cystic fibrosis patients, lung function deteriorates because of bacterial colonisation resulting in persistent infection and secondary airway obstruction.

As expected, higher Sao$_2$ levels correlated well with good clinical status and low radiological scores. In patients with cystic fibrosis with better weight gain, there is also a higher Sao$_2$. Poor nutritional state is related to decreased resistance to infection with subsequent decline in pulmonary function.

CONCLUSIONS

Sao$_2$ measurements are a useful addition to the clinical and lung function assessment of cystic fibrosis patients. They correlate well with clinical status and other more specific methods of assessment including radiology and nutrition. Although they do not replace basic measurements with less complicated apparatus such as the spirometer, they do represent the final common pathway of oxygen delivery to the tissues. Although not recommending that every cystic fibrosis clinic should have an oximeter, the ability to utilise such measurements either individually or longitudinally will become increasingly valuable in the future care and management of these patients.

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Baby Check and the Avon infant mortality study

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Abstract

Thirty seven sudden, unexpected infant deaths from the Avon study were scored retrospectively for serious illness using a modified version of Baby Check. Three cases (8%) scored very highly. In a small proportion of sudden deaths, Baby Check could have identified serious illness before death and led to hospital admission.

Baby Check is a scoring system to help parents and doctors quantify serious illness in babies up to 6 months of age.[1] It is based on seven symptoms and 12 signs, each of which has a particular score. The individual scores are added together to give an overall score, and the higher it is the more ill the baby. Scores below 8 indicate 'the baby is well or only mildly ill and is not likely to need medical attention at the moment'. Between 8 and 12 'the baby is unwell but not likely to be seriously ill—contact your doctor, health visitor or midwife for advice'. Between 13 and 19 'the baby is ill and needs to be seen by a doctor'. If the score is 20+ 'the baby may be seriously ill and needs to be seen by a doctor straight away'.

A proportion of babies dying suddenly and unexpectedly may be seriously ill before they die, but with unrecognised symptoms.[2] To investigate this, the mothers of Avon infants who died suddenly and unexpectedly during a period of nine months, and two age matched controls, were asked about their baby's symptoms and signs in the 24 hours before the baby's death or interview respectively.

Methods

The mothers of 38 infants who died suddenly and unexpectedly and 76 matched controls[3] were interviewed. Using questions based on Baby Check, all but four items were scored retrospectively: rectal temperature, big toe squeeze, hernia, and crying during assessment. One 12 month old infant who died and his two controls were excluded from the analysis.

Results

Table 1 gives the distribution of Baby Check scores by illness grade for the sudden deaths and for the controls. Eleven per cent of babies in each group scored 8+, but only one control (1%, score 20) as against three of the infants who died (8%, scores 26, 33, and 44) scored 20+. All the infants who died were clearly ill, while the controls were apparently well (table 2).

Table 1 Distribution of Baby Check scores in 37 infants dying suddenly and unexpectedly and 74 age matched controls

Illness grade	*Score range*	*No (%) cases*	*No (%) controls*
Well/mildly ill	0–7	33 (89)	66 (89)
Needs advice	8–12	—	4 (5)
Needs to be seen	13–19	1 (3)	3 (4)
Needs to be seen urgently and probably admitted	20+	3 (8)	1 (1)

Table 2 Babies with Baby Check scores of 13+

Score	*ID*	*Group*	*Findings (*indicates 'explained' death)*
44	80	Case	*Intracranial haemorrhage and gastrointestinal bleeding (two day history)
33	79	Case	**Staphylococcus aureus* septicaemia and pyelonephritis (16 hour history)
26	94	Case	Adenovirus type 5 isolated from nasopharynx
20	95B	Control	Nothing significant, no medication, saw doctor two weeks earlier
16	95A	Control	Nothing significant
15	80A	Control	Reported as having laryngeal stridor from soon after birth
14	72	Case	Respiratory syncytial virus isolated from nasopharynx and trachea
13	82B	Control	Nothing significant

Discussion

A minority of infants dying suddenly and unexpectedly had signs and symptoms consistent with serious illness. Eight per cent of the infants who died appeared to be seriously ill, appreciably less than the 24% found in Knowelden's report,[2] with at least five separate symptoms/signs and Baby Check scores of 26+. In field trials of babies brought to hospital,[4] scores of 20+ had a 67% predictive value for needing hospital treatment. Scores of 33 or 44 were rare even in paediatric outpatients, with a 100% predictive value for hospital treatment. Had these high scoring babies been taken to hospital they would probably have been admitted, and might not have died.

Two victims (79 and 80, table 2) were 'explained' deaths, with clear cut pathology. The other two 'explained' deaths were a baby with a perforated stomach, who was asymptomatic when put to bed, and a baby with heart failure due to an atrioventricular canal defect, who was always mildly cyanosed and breathless. Both babies scored low. The third high scoring case (94, table 2) was not an 'explained' death, but adenovirus was isolated at postmortem examination.

Fewer control babies scored 0–7 (89%) than in the Baby Check field trials of mothers at home (97%).[5] Here the mothers did not see the explanations in the Baby Check booklet, so they probably used less stringent criteria for each symptom/sign, and overscored. All three controls scoring 13–19 (table 2) had either green vomit (13 points) or recession (15 points), which are very rarely seen in the community. These would probably have been reported absent with Baby Check, where parents are told not to score items if in doubt.

The results suggest that Baby Check could help parents recognise a small proportion of babies at risk of sudden unexpected death. Babies who die suddenly and unexpectedly are more likely to be taken to the general practitioner in the week before death than control babies.[6] This difference is unrelated to reported symptoms, but parents clearly react to their perception of the babies' well being. If such families used Baby Check they might be empowered to obtain timely medical help, so that some of the babies would not die.

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Guillain-Barré syndrome in three siblings less than 2 years old

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Abstract

Three of five children who were born to consanguineous parents developed Guillain-Barré syndrome before they were 3 years old. The syndrome is rare in early childhood and we suggest that there may be a genetic element in the pathogenesis.

Polyradiculoneuritis (Guillain-Barré syndrome) has become the most common form of acute paralysis since the decrease in the incidence of poliomyelitis.[1] Though the incidence in children seems to be increasing, it is still rare below the age of 2 years.[2–3] There have been only three reports of familial Guillain-Barré syndrome in adults, and none in children, to our knowledge.[4–6]

We describe three siblings from a consanguinous marriage who developed Guillain-Barré syndrome when they were less than 2 years old. The parents were young, healthy Arab Moslems who were second cousins and had five children (three boys and two girls). Their second, fourth, and fifth children are described in this report; the other two have always been healthy.

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Case reports

CASE 1

A 2 year old boy was admitted to another hospital in 1980 with progressive weakness and difficulty in swallowing. Two weeks before admission he had a short febrile illness and a cold. On admission he was pale and in a 'poor general condition', with drooling, generalised hypotonia and hyporeflexia. Results of laboratory tests did not indicate a diagnosis.

The child was treated with corticosteroids and intravenous fluids replacement. His condition deteriorated and he died on the sixth day in hospital with the presumptive diagnosis of encephalitis.

CASE 2

The younger sister of case 1 was admitted to this hospital in 1984 at the age of 22 months because of weakness in the lower limbs. One week before admission she had had pharyngitis, and subsequently she became sleepy and developed unstable gait. Neurological abnormalities included ataxic gait, inability to stand, and areflexia. Examination of the cerebrospinal fluid showed no cells, glucose 3·1 mmol/l, and a protein concentration of 1·6 g/l. The electroencephalogram was interpreted as normal. Electromyography showed reduced nerve conduction velocity with prolongation of distal motor latency. Poliomyelitis was ruled out. HLA typing failed to show the DR3, A3, and B8 antigens.

Within a week she started to improve spontaneously, and at follow up examination two years later she had no neurological deficit.

CASE 3

The younger brother of case 2 was admitted to the paediatric intensive care unit in 1987 at the age of 9 months with respiratory failure following progressive generalised weakness. Two weeks before admission he had had an episode of fever and rhinorrhea. On admission he was fully awake and had pronounced hypotonia with flaccid, almost complete, paralysis of all extremities. Deep tendon reflexes were absent. Examination of cerebrospinal fluid showed no cells. Concentration of protein was 0·6 g/l, glucose 2·9 mmol/l, and myelin basic protein 0·16 g/l (normal <0·07). He had a strong positive reaction to oligoclonal antibodies to central nervous system proteins. Red cell cholinesterase was 12·8 IU/ml (within the reference range). Electromyography showed severe neuropathy and a peripheral nerve demyelinisation pattern. Culture and antibody screens of cerebrospinal fluid were negative for all viruses, and tissue typing did not show the DR3, A3, or B8 antigens.

The child's general and neurological condition improved gradually, and he was weaned from mechanical ventilation after 40 days. Subsequently he showed slight but slow improvement, but at 3·5 years of age he had pronounced hypotonia, areflexia in all limbs, and was unable to stand or walk unsupported.

Discussion

The clinical features and laboratory findings in cases 2 and 3 fitted the criteria for Guillain-Barré syndrome.[1] They had the typical cyto-albumin dissociation and peripheral nerve demyelinisation pattern on nerve conduction studies. Case 1 presented with a clinical picture identical to that of case 3, and we suspect that he died of respiratory failure caused by respiratory muscle paralysis and that the diagnosis of encephalitis was wrong.

Other possible causes of acute onset muscle weakness, such as poliomyelitis, diphtheria, botulism, and poisoning by organophosphates, lead, or hexacarbons were ruled out by the history, results of laboratory tests, and clinical course.

Guillain-Barré syndrome occurs rarely in infancy and early childhood.[2–3] In a series of 30 children with Guillain-Barré syndrome only three were less than 2 years of age and in the series of Peterman *et al* only three of 26 were less than 2 years of age.[3] The youngest patient in a recent series of 157 cases from Massachusetts General Hospital was 8 years old.[2] Patients younger than 1 year of age (as case 3) were not reported.

Familial Guillain-Barré syndrome has not to our knowledge been reported in children, and we could find only three instances in adults.[4–6] Two elderly siblings with painful, slow onset paralysis of all four limbs and raised concentrations of protein in the cerebrospinal fluid have been described.[4] However, symptoms were initially sensory (severe pain in the lumbar region and buttocks), progressed over months, and were not associated with autonomic dysfunction. Such findings do not fit well with the diagnostic features established by the Guillain-Barré syndrome study group.[1] Another report described a father and a 24 year old daughter whose presentations were compatible with Guillain-Barré syndrome.[5] A third report described two brothers who acquired a paralytic disease while working in Gabon and taking chloroquine[6]; both had raised concentrations of protein in the cerebrospinal fluid.

The occurrence of such a rare disorder in three siblings born to healthy, consanguineous parents suggests the presence of a genetic defect that is transmitted in an autosomal recessive way. An abnormal immune response against the peripheral nervous system has been implicated in the pathogenesis of the Guillain-Barré syndrome. The syndrome is often triggered by a previous viral infection or by certain immunisations. It has clinical and pathological features similar to those found in experimental allergic neuritis, which is an autoimmune disease that can be produced in animals by injecting peripheral nerve antigens. The considerably increased concentrations of immunoglobulin in the cerebrospinal fluid, sometimes with raised oligoclonal bands (as in case 3) also imply an alteration in local immunoregulation. Lymphocyte reactivity to myelin components of peripheral nerves has been reported in patients with Guillain-Barré syndrome, but the evidence that the pathogenesis has an immunological basis is indirect and circumstantial.

Disorders associated with immune abberations are sometimes related to the HLA system. A few studies have reported an increased incidence of class I A3 and B8 and class II DR3 antigens in Guillain-Barré syndrome.[7] As these specific antigens were not isolated in this family, the HLA system cannot be implicated.

This evidence suggests that genetic factors may have a role in the still uncertain aetiology of this disorder.

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Encephalomyelitis with seroconversion to *Listeria monocytogenes*

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Abstract

A previously healthy girl recovered from a lymphocytic encephalomyelitis with brain stem involvement after antibiotic and steroid treatment. Cultures of blood and cerebrospinal fluid were negative, but she seroconverted to *Listeria monocytogenes* serotype 4. Antilisterial treatment should be considered in similar cases.

Acute meningoencephalitis with a scanty cerebrospinal fluid lymphocytosis, normal cerebrospinal fluid glucose and protein concentrations, and a normal computed tomogram is usually considered to be viral. In adult patients listerial infection is a recognised cause, especially if there is brain stem involvement, but this has not been described in children.[1]

Case report

A 10 year old girl with an unremarkable medical history presented to another hospital with a four day history of headache and malaise, which was treated as sinusitis for two days with oral amoxycillin. Fever, herpes labialis, neck stiffness, and mild confusion were noted, but no focal signs. Her cerebrospinal fluid had 22 lymphocytes/ml, with normal glucose and protein concentrations and no growth on culture. Over the next 24 hours she became dysarthric and incontinent. On transfer (day 1) she was unresponsive to command, with flexor withdrawal from pain, mild neck stiffness, early papilloedema, sluggish pupil responses to light, trismus, hyperreflexia in the arms, diminished tone in the legs, and generalised high voltage delta activity in her eletroencephalogram. Computed tomography showed no focal lesion and no evidence of raised pressure. She was treated with intravenous benzylpenicillin and chloramphenicol for five days and acyclovir for 10 days. Over the next two days she developed obligate doll's eye movements and a right abducens palsy. Repeat lumbar puncture showed pressure of 10·5 cm H_2O (1·03 kPa) and 67 lymphocytes/ml, with no growth. On day 4 she had a respiratory arrest, leading to assisted ventilation for two weeks. She also developed a complete flaccid paraplegia with urinary retention. At this point she was started on dexamethasone, which was continued for one week and then weaned over one week. On day 7 she opened her eyes spontaneously and moved her left hand to command. On day 10 she became feverish again and was treated with intravenous amoxycillin for *Escherichia coli* in her urine. A repeat computed tomogram was unchanged. Her conscious level and motor function gradually improved. On day 17 nerve conduction velocity and evoked amplitudes were normal but F responses were few or absent. Between days 22 and 28 she was lifting both arms to command and communicating by sign language, but had obligate doll's eye movements, brisk jaw jerk, bilateral facial palsy, palatal weakness, poor cough, a flaccid paraplegia, and absent pin prick sensation from T8 to T12. By day 40 she was communicating verbally with no evidence of intellectual deficit, could write legibly, but had appreciable emotional lability, mild left facial and palatal weakness, and an asymetrical mainly distal paraparesis and needed a frame to walk. By day 95 she only had minimal signs of a left hemiparesis.

Bacterial and viral culture of cerebrospinal fluid, blood, and stool were all negative. There were no change in blood and cerebrospinal fluid titres to herpes viruses, mycoplasma, or borrelia. Blood taken on days 1 and 9 showed a rise in titre to *Listeria monocytogenes* type 4 from <16 to 32, which is regarded as seroconversion.

Discussion

This is the first case we can find associating *L monocytogenes* infection in a child with encephalitis involving the brain stem, myelitis and possible radiculitis, suggested by the abnormal F responses. In children listerial infection of the nervous system usually causes meningitis.[2] In adults a range of disease is reported, including meningitis, meningoencephalitis, which is distinguished by the presence of focal signs, and rhombencephalitis, where only the brain stem is affected.[1 3 4] The meningitic form usually has a cerebrospinal fluid polymorphonuclear leucocytosis (approximately 2000/ml), low glucose and high protein concentrations in the cerebrospinal fluid, and positive blood and cerebrospinal fluid cultures. The meningoencephalitic form has a lower, predominantly lymphocytic, cerebrospinal fluid cell count (approximately 200/ml), frequently normal glucose and protein concentrations in the cerebrospinal fluid and the cerebrospinal fluid or blood is culture negative in 25% of cases.[3] The rhombencephalitic form usually show only a scanty cerebrospinal fluid lymphocytosis and culture is usually negative, and the diagnosis is based on positive blood cultures, which can also be repeatedly negative in some patients. Reported cases of rhombencephalitis have a high mortality (30%) and a characteristic postmortem feature is the presence of microabscesses.[4 5] There is one case

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report of an unusual relapsing rhombencephalitis associated with seroconversion to *L monocytogenes*.[5] Until recently serological diagnosis has been unreliable because of cross reacting antibodies, but the present assay, only available at the Public Health Laboratory Service (PHLS) in Colindale in the UK, is more accurate and seroconversion is suggestive of disease.

Our patient had severe brain stem involvement but differed from the above descriptions in having myelitis as well. Acute demyelinating encephalomyelitis has not to our knowledge been associated with listerial infection and would be difficult to distinguish from microabscesses by imaging or evoked potentials. Partially treated meningitis and the brain stem encephalitis described in children by Bickerstaff have different clinical features.[6] Other causes of a lymphocytic encephalitis were excluded.

We recommend that any child with focal brain stem and/or spinal cord signs and a cerebrospinal fluid lymphocytosis, with or without encephalitis, should be treated with high dose intravenous ampicillin and gentamicin until listerial infection has been excluded.

We thank Dr McLauclin, Central PHLS, Colindale Avenue, London for the serological assay.

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No sensory neuropathy during pyridoxine treatment in homocystinuria

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Abstract

Seventeen patients with cystathionine synthase deficiency homocystinuria were examined clinically and neurophysiologically for evidence of sensory neuropathy. All had received high dose pyridoxine (vitamin B–6) for many years. Absence of neurological disturbance in all cases suggests long term treatment with pyridoxine in the dosages used in homocystinuric patients is not harmful.

Homcystinuria due to cystathionine synthase deficiency, an autosomal recessive disorder of methionine metabolism, results in mental, ocular, skeletal, and vascular disease if untreated. About half of the patients respond to treatment with pharmacological doses of pyridoxine (vitamin B–6).[1] In our experience unresponsive patients can be managed effectively with a diet low in methionine. We have also given pyridoxine to patients with no clear response to the vitamin on the basis that the exact mechanism of pyridoxine responsiveness is unknown and the assessment of partial responsiveness is difficult. High dose pyridoxine is reported to be associated with sensory neuropathy.[2] Reports of toxicity in humans on relatively low pharmacological dosages (200 mg/day)[3] have alerted us to the possibility of pyridoxine toxicity in patients with homocystinuria.

Seventeen patients with homocystinuria (eight clearly pyridoxine responsive) who had been treated with large doses (200–600 mg/day) of pyridoxine over many years (10–24 years) were examined clinically and neurophysiologically for evidence of neuropathy.

Patients and methods

All patients were under the care of the Willink Biochemical Genetics Unit. Sex, age at diagnosis, pyridoxine responsiveness, daily dosage, and duration of treatment are shown in the table.

Inquiry was made about sensory symptoms, including difficulty handling objects, absence of. sensation leading to unnoticed injury, weakness, and problems with balance and walking. Physical examination looked specifically at touch (cotton wool), pain (pin prick), proprioception, Romberg's sign, tendon reflexes, and observation of gait.

Plasma concentrations of pyridoxal phosphate were measured by high performance liquid chromatography.[4]

Electrophysiological studies were performed to look for possible subclinical effects of pyridoxine on the peripheral nerves. A supramaximal stimulation of 0·1 ms duration was delivered at 1 second intervals, using surface electrodes (ring electrodes for finger stimulation). The median (index finger to wrist) and sural (calf to lateral malleolus) sensory potentials were recorded using surface electrodes. Onset to latency (ms), peak to peak amplitudes (uV), and sensory conduction velocity (m/s) were measured. The median and lateral popliteal motor responses were recorded over abductor

Details of 17 patients studied

Patient No	*Sex*	*Age at diagnosis*	*Response to pyridoxine*	*Daily dose of pyridoxine (mg)*	*Duration of treatment (years)*	*Plasma concentration pyridoxal phosphate (nmol/l)*	*Motor conduction velocity (N1) (m/s)*	*Sensory nerve conduction (N2) μV)**
1	M	13 years	Yes	200	7	1337	39	10
2	F	18 years	Yes	200	9	1014	47	15
3	F	10 years	Yes	200	10	882	44	10
4	F	19 days	None	300†	11	166	49	12
5	F	14 days	None	300	14	1123	50	20
6	M	17 days	Part	400	14	636	52	10
7	F	12 days	None	300†	15	29	48	15
8	M	14 days	Part	400	16	585	58	10
9	F	20 days	None	300	16	1451	51	10
10	M	30 days	None	450	18	402	49	20
11	M	10 days	None	400	18	618	49	15
12	M	7 years	None	300	19	1352	39	10
13	F	10 years	Yes	500	20	1390	53	10
14	F	14 years	Yes	500	21	1347	50	13
15	F	10 years	Yes	200	22	781	51	15
16	M	7 years	None	400	22	478	44	10
17	F	3 years	Yes	200	24	1582	41	10

*Nerve conduction was also performed in the upper limbs, all results were normal. In this table the results from left lateral popliteal nerve (motor conduction, N1) and the left sural nerve (sensory amplitude, N2) are shown.

†Non-compliance.

Normal ranges: pyridoxal phosphate 20–50 nmol/l, motor conduction velocity (NI) 40–56 m/s, and sensory nerve conduction (N2) >5 μV.

pollicus brevis and extensor digitorum brevis respectively after stimulation of the median nerve at wrist and elbow and the lateral popliteal nerve at ankle and fibular head. Distal and proximal latency (ms), compound muscle potential amplitude (negative component, mV), and motor conduction velocity (m/s) were recorded.

Results

Inquiry indicated no symptoms suggestive of neuropathy in any of the patients and physical examination was normal in all cases. Plasma concentrations of pyridoxine metabolites and the results of electrophysiological studies are shown in the table.

Very high plasma concentrations of pyridoxine and pyridoxal phosphate in most patients confirmed compliance with treatment, at least at the time of study. This indicates adequate uptake of pyridoxine, conversion to pyridoxal phosphate, and maintenance of high concentrations of these compounds. In two patients with much lower concentrations of vitamers poor compliance was confirmed after direct questioning.

Nerve conduction was completely within the normal range for each of the four nerves studied.

Discussion

Evidence of peripheral neuropathy was first reported in seven adults aged 20–43 years receiving 2–6 g/day of oral pyridoxine for periods of two to 40 months.[2] In a less detailed study in which some subjects were not clinically examined evidence of neuropathy was reported in 16 subjects receiving 0·2–5·0 g of pyridoxine daily, notably in three subjects receiving 200, 500, and 500 mg/day respectively, for eight months to three years.[3] In a review based on a literature survey it was concluded that pyridoxine administration below 500 mg/day appears to be safe,[5] although this was based on treatment periods of only up to six years and takes no account of intake related to body weight.

In our study daily doses are less than those reported to cause neuropathy. However these doses related to body weight ranged from 10–90 mg/kg/day during the the first 10 years of life, which is closer to the 25–120 mg/kg/day (based on assumed body weights) in adults reported by Schaumburg *et al.*[2] Also our homocystinuric patients received pyridoxine for 7–24 years (mean 16 years), which is far longer than in previous reports. Therefore the finding of no evidence of neuropathy by extensive clinical and neurophysiological studies is reassuring. This suggests that long term treatment of homocystinuria with doses up to 800 mg of pyridoxine per day is not harmful.

Differences in handling and storage of pyridoxine vitamers between adults and children or in cystathionine synthase deficiency are unlikely. In fact pyridoxal phosphate concentrations in our compliant patients ranged from 8–32 (average 20) fold higher than the upper limit of the control range. This is higher than the 6–7 fold increase of pyridoxal phosphate reported in six healthy adults receiving 100 mg oral pyridoxine/day.[6] Despite these reassuring results careful thought should be given to the class of homocystinuric patient treated with pyridoxine and the amount prescribed. The justification for giving patients who are unresponsive to pyridoxine large amounts of the vitamin must be questioned. In patients who are responsive to pyridoxine the smallest dosage compatible with good biochemical control (absence of homocystine from plasma) should be recommended.

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Typhoid fever, ciprofloxacin, and renal failure

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Abstract

An 11 year old boy from whom *Salmonella typhi* had been isolated was treated with ciprofloxacin. He developed non-oliguric acute renal failure that was treated successfully.

Ciprofloxacin has recently been suggested as the preferred treatment for traveller's diarrhoea and multiresistant *Salmonella typhi* infection.[1] The latter problem is being seen increasingly often in the United Kingdom.[2] Although the drug is not recommended for children, it is an accepted oral treatment for pseudomonal infections, particularly infective exacerbations of cystic fibrosis.[3] We report a case of non-oliguric acute renal failure caused by interstitial nephritis that developed after treatment of typhoid fever with ciprofloxacin.

Case report

An 11 year old boy was admitted with a four day history of pyrexia, rigors, diarrhoea, and vomiting. He had returned 10 days earlier from a month's holiday in Pakistan. He had received no immunisation against typhoid or cholera and no prophylaxis against malaria. The *S typhi* phage type M1 that was isolated from his blood and stools was resistant to ampicillin, trimethoprim, and chloramphenicol but sensitive to cefuroxime, gentamicin, and ciprofloxacin. The boy was 152 cm tall and weighed 32·7 kg.

Chloramphenicol was prescribed for one day, gentamicin for two days (7·3 mg/kg body weight/day), and cefuroxime (90 mg/kg body weight/day) for seven days. Three days after starting cefuroxime his fever had not settled and ciprofloxacin was added as this antibiotic was felt to be more bactericidal in a resistant *S typhi* infection. Two initial doses of oral ciprofloxacin were followed by six days of intravenous treatment, the dose being 150 mg twice a day (9 mg/kg body weight/day) with a further two days of oral treatment (15 mg/kg body weight/day). The child's fever settled within 36 hours of starting ciprofloxacin.

The plasma urea and creatinine concentrations before treatment were 3·7 mmol/l and 74 μmol/l, respectively. Analysis of urine on admission showed neither blood nor protein. The patient initially responded well, but two weeks later he developed lethargy and anorexia with occasional vomiting. The urea and creatinine concentrations had risen to 37 mmol/l and 1183 μmol/l, respectively. He continued to pass urine, which now showed moderate glycosuria, haematuria, and proteinuria, with no casts or crystals. The blood film did not show any eosinophilia, the haemoglobin concentration was 87 g/l, and the white cell count $6{\cdot}3\times10^9$/l. Ciprofloxacin was discontinued, but after a week of further observation and conservative management his plasma creatinine concentration remained at 1133 μmol/l.

A percutaneous renal biopsy was done, which showed clear evidence of interstitial nephritis (figures 1 and 2). There was no evidence of immunoglobulin or complement deposition on immunofluorescent staining and electron microscopy of the glomeruli showed no abnormality. Prednisolone 70 mg daily (2·1 mg/kg body weight/day) was given orally for three days and tapered off over a week when the plasma creatinine concentration had fallen to 155 μmol/l. There was no recurrence of the typhoid fever and two weeks later the creatinine concentration had fallen to 79 μmol/l.

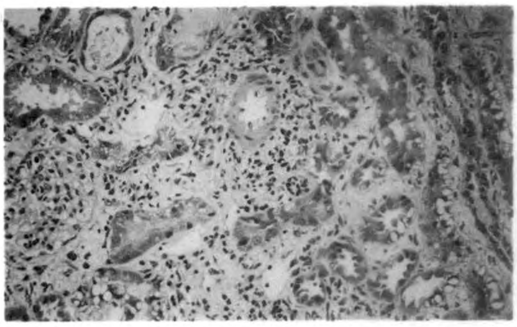

Figure 1 Photomicrograph of a renal biopsy specimen at a magnification of 260 showing interstitial nephritis with pronounced oedema and mixed infiltrate of chronic inflammatory cells.

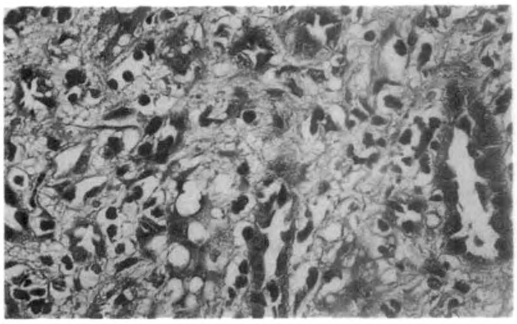

Figure 2 Photomicrograph of a renal biopsy specimen at a magnification of 650 showing acute interstitial nephritis with a mixed chronic inflammatory cell infiltrate and invasion of tubules by lymphoid cells.

Discussion

The clinical course in this case is consistent with ciprofloxacin induced interstitial nephritis

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causing non-oliguric renal failure. This has been described in a few case reports.[4–6] In only one patient was the diagnosis proved on histological examination,[4] and there have been no cases reported in children to our knowledge. Although our patient also received cefuroxime we are unaware of any cases of interstitial nephritis induced by cefuroxime given either alone or with other drugs.

Ciprofloxacin is one of a relatively new group of antimicrobial agents, the quinolones, the indications for which are increasing. Many side effects have been reported and the drug, like others in its class, is not recommended for children and adolescents because of the reported arthropathy in weight bearing joints of immature animals. Range of activity of ciprofloxacin and availability in an oral form has made it an attractive choice for the treatment of pseudomonal and other infections, particularly in patients with cystic fibrosis and urological problems.

All patients with ciprofloxacin associated renal failure described by the time of writing have maintained a urine output. Detection therefore depends upon biochemical tests. We suggest that renal function should be monitored during treatment with ciprofloxacin. In addition, ciprofloxacin should be added to the long list of drugs that may cause interstitial nephritis.

We thank Dr S Boyd for providing the photomicrographs.

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Down's syndrome

The April issue of *Developmental Medicine and Child Neurology* contains three articles about Down's syndrome. In the first of these, Cliff Cunningham and his coworkers (pages 285–95) report on 123 children and their families in Manchester addressing the question of whether development and social adaptation are related to appearance. Checklists completed by teachers were used to assess appearance and 'attractiveness' and child and family functioning were measured by psychologists and from data obtained from parents by questionnaire and interview. The authors conclude that physical appearance is not a major determinant of development or social functioning in Down's syndrome and that their findings would not support attempts to alter the appearance by surgery. A possible drawback of the study is that the assessments of appearance and attractiveness were done by teachers and therefore might not be devoid of bias vis-a-vis the viewpoint of the general population.

The second paper is from Munich (GJ Limbrock and colleagues, pages 296–303) and describes the use of Castillo-Morales' orofacial therapy in which a 'manual stimulation and facilitation programme' is combined with the use of an oral plate designed to stimulate the palate, tongue, and lips. I suspect that this is the kind of treatment which needs to be seen in action in order to get to grips with it. I found that the results were presented in a way which was difficult to assess but 67 children were treated and the authors claimed significant improvements in tongue position, lip tone, mouth closure, drooling, and sucking. Unfortunately the study was uncontrolled.

The third paper is about the attitudes of American doctors to the treatment of duodenal atresia in Down's syndrome (Mark L Wolraich and colleagues, pages 336–42). They surveyed a sample of paediatricians, paediatric surgeons, and general practitioners and found that more would recommend surgery than has been the case in the fairly recent past. Perhaps not surprisingly the surgeons tended to be the least optimistic about prognosis and the least likely to recommend surgery.

ARCHIVIST

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CURRENT TOPICS

How can the work of junior paediatricians be reduced?

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In 1989 the British Postgraduate Medical Federation (BPMF) issued a report which voiced concern about the pattern of junior staffing in paediatrics.[1] The report, which was based on a survey in five districts, found that junior staff in paediatrics work for longer hours than in other specialities, are the busiest doctors in a hospital at night, and are the most likely to have an interrupted night while on duty. The BPMF report, and a subsequent agreement by the ministerial group on junior doctors' hours,[2] have called for research as to how the volume of work can be reduced and, in particular, whether some tasks might either be postponed until morning or delegated to other professionals. We report the results of such a study.

Methods

The study was performed in two phases. In the first phase the tasks undertaken by junior doctors in four NHS hospitals were identified. These included one teaching hospital and three district general hospitals, in inner and outer London and in a rural district about 50 miles from London. Paediatric junior staff used diaries, designed after a pilot study in one of the hospitals, to record all activities undertaken between 5pm and 9am over a seven day period. Diaries were completed by eight senior house officers, two registrars, and a senior registrar. The information recorded included whether the activity was self initiated or as a result of a request from other staff, the time of commencement, details of the request, and the activity undertaken. The doctors described the activities in their own words. These data were supplemented by interviews with five senior house officers and a registrar and by comments from a meeting attended by all grades of medical staff and nurses in a paediatric department in one of the hospitals concerned. A report was compiled using information collected during this phase, supplemented with a review of relevant literature.

In the second phase, a panel of relevant professionals was established. It was composed of: six consultant paediatricians, two consultant obstetricians, and a paediatric senior house officer. The consultants were selected from hospitals throughout the region.

A nominal group technique described by Glaser was employed.[3] Approximately six weeks before the date of the panel meeting each participant was sent (i) the report which had been produced in the first phase of the study, (ii) a review of current concerns about the work of junior doctors and arguments for and against the existing system, and (iii) a first round questionnaire which sought panellists' views as to the appropriateness of a paediatrician performing certain tasks at night.

Appropriateness was scored on a nine point scale, with 1 meaning the task was totally inappropriate for a non-medical member of staff and 9 meaning it would always be appropriate for a non-medical member of staff to perform the task. The responses to the questionnaire were collated and at the panel meeting each participant was provided with a new copy of the questionnaire in which the group responses were indicated. The meeting was chaired by one of us (NAB) and lasted about three hours. Participants were given lunch and reimbursed for travelling expenses, but there was no other payment. After an introductory explanation, each item on the questionnaire about which there were a variety of opinions was discussed. At the end of the discussion on each question panellists were again asked to score the task on a scale from 1 to 9. There was no pressure on panellists to reach consensus.

The responses were analysed for agreement or disagreement and a record of the discussion was transcribed. Agreement was deemed to be present when, after discarding the single highest and lowest scores, the remaining scores of all nine panellists lay within a three point range. Disagreement occurred when, after discarding the single highest and lowest scores, at least one of the remaining seven scores was 1–3 and at least one was 7–9. All other results were designated as partial agreement. The rationale for this scoring system has been described elsewhere.[4]

Results

QUANTITATIVE DESCRIPTION OF TASKS

It was not possible to distinguish with certainty between activities relating to general and those relating to neonatal paediatrics. This was mainly because of the organisation of the service. In hospital C both are covered by a single senior house officer although the facilities are on sites which are several miles apart, whereas in hospitals A, B, and D, separate senior house officers cover general and neonatal paediatrics. They are also on separate sites in districts B and D. In all cases a single registrar covers both components when on duty, although in district

B that individual also covers hospitals in neighbouring districts.

Clinical tasks, such as admitting and reviewing children, resuscitating infants, and prescribing, constituted 44% of recorded activities (table 1). The next most frequent category, comprising 19% of activities, consisted of a series of technical tasks of varying complexity. This was followed by giving and receiving advice. As expected, this was a major component of the work of registrars. Finally clerical tasks and attendance at deliveries each comprised approximately a tenth of recorded activities.

INTERHOSPITAL COMPARISONS

The small number of respondents precluded quantitative comparison between hospitals. However, qualitative differences in policy on the requirement for a paediatrician to be present at a delivery and the division of tasks between doctors and nurses were obtained (tables 2 and 3).

ATTITUDES OF JUNIOR STAFF

Paediatric junior staff demonstrated considerable dissatisfaction largely because of the intensity of work. Some specific issues were raised involving work which was seen to be unnecessary. The principal issue involved attendance at deliveries. They saw their role at most deliveries as precautionary, which was largely inevitable because of the difficulty in predicting which infants would require their assistance. However, several questioned whether a paediatrician should routinely be called to certain types of delivery. Conversely some senior house officers recalled situations where they had not

Table 1 Analysis of activities from diaries completed by junior doctors (column percentages in parentheses)

	Senior house officer	*Registrar*	*Senior registrar*	*All*
No of diaries	8	2	1	11
(1) Clinical tasks:				
Resuscitate child	16 (7)	2 (5)	2 (13)	20 (7)
Review patient in ward	25 (11)	10 (23)	2 (13)	37 (13)
See patient in accident and emergency	29 (13)			29 (10)
Admit to SCBU/NNU	7 (3)	3 (7)	1 (6)	11 (4)
Clerk patient	12 (6)			12 (4)
Prescribe drugs	6 (3)			6 (2)
Prescribe intravenous fluids	3 (1)			3 (1)
Order *x* ray films	3 (1)			3 (1)
Monitor baby awaiting transfer		1 (2)		1 (0)
Subtotal	101 (46)	16 (37)	5 (18)	122 (44)
(2) Technical tasks:				
Blood sample				
Arterial	12 (6)	2 (5)		14 (5)
Venous	9 (4)	3 (7)		12 (4)
Re/site intravenous infusion	8 (4)	2 (5)	1 (6)	11 (4)
Give intravenous drugs	4 (2)			4 (1)
Septic screen	2 (1)	1 (2)		3 (1)
Analyse blood for bilirubin	4 (2)			4 (1)
Insert chest drain		2 (5)		2 (1)
Lumbar puncture	1 (0)			1 (0)
Add drugs to infusion	1 (0)			1 (0)
Exchange transfusion (neonate)		1 (2)		1 (0)
Insert nasogastric tube	1 (0)			1 (0)
Subtotal	42 (19)	11 (25)	1 (6)	54 (19)
(3) Advice:				
Consult with other doctor	19 (9)	9 (20)	6 (38)	34 (12)
Talk to relatives	4 (2)	3 (7)		7 (3)
Advise nurses by phone	2 (1)	1 (2)		3 (1)
Advise general practitioner by phone	1 (0)			1 (0)
Reassure patient	1 (0)			1 (0)
Subtotal	27 (12)	13 (30)	6 (38)	46 (17)
(4) Administrative clerical tasks:				
Complete accident form	1 (0)			1 (0)
Dictate discharge summaries	2 (1)		1 (6)	3 (1)
File results	1 (0)			1 (0)
Liaise with other agency	8 (4)			8 (3)
Organise beds	3 (1)			3 (1)
Organise blood transfusion	3 (1)			3 (1)
Pursue results	1 (0)		1 (6)	2 (1)
Teaching	1 (0)		1 (6)	2 (1)
Subtotal	20 (9)		3 (19)	23 (8)
(5) Attend delivery	28 (13)	4 (9)	1 (6)	33 (12)
Total	218 (100)	44 (100)	16 (100)	278 (100)

SCBU/NNU, special care baby unit/neonatal unit.

Table 2 Variations in practice between four hospitals (A, B, C, and D) regarding tasks undertaken by junior doctors

Task	*A*	*B*	*C*	*D*
Give intravenous drugs	First dose only	Yes	First dose only	Midnight doses only
Add additives to infusions	No	Yes	No	No
Supervise blood transfusions	No	Yes	No	No
Take blood samples	No	Yes	No	Yes

Source: interviews with junior doctors.

Table 3 Circumstances in which a paediatrician is present at birth between four hospitals (A, B, C, and D)

Task	*A*	*B*	*C*	*D*
Forceps delivery	Yes (including lift out forceps)	Yes	Yes	Yes
Intrapartum fetal distress	Yes	Yes	Yes	Yes
Caesarean section	Yes	Yes	Yes	Yes
Meconium staining	Yes	Yes	Yes	Yes
Severe growth retardation	Usually (often called after birth)	Yes	Yes	Usually (often called after birth)
Maternal diabetes	Yes	Yes	Yes	No
Rhesus incompatibility	Yes	Yes	Yes	Called after birth
Fetal abnormalities	Called after birth	Sometimes	Yes	Yes
Multiple births	Yes	Yes	Yes	Yes
Profuse vaginal bleeding	Yes	No	No	No
Abnormal presentation	Yes	Yes	Yes	Yes

Source: interviews with junior doctors.

been called because a member of the delivery team was sufficiently confident at resuscitation. In particular, some midwives were much more willing to resuscitate babies than others, and a few instances were recalled when midwives had undertaken intubation. On other occasions a paediatrician was not called because the obstetric senior house officer had neonatal experience. This was especially relevant in the one hospital, where doctors perform a higher proportion of normal deliveries than in other hospitals, although in another, where virtually all normal deliveries are carried out by midwives, one paediatrician expressed slight annoyance about being called to many deliveries when the obstetric senior house officer was not.

There was also irritation about being called long before a delivery occurs. They accepted that the duration of labour is often unpredictable, but paediatricians were often called to caesarean sections at the same time as anaesthetists, with a lengthy delay before the baby is born. This leads to postponement of other work.

They drew attention to the complexity of treating neonates. This was substantiated by several episodes recorded in diaries where a single child occupied a senior house officer for up to six hours. Support from registrars was a problem where neonatal units and general paediatric wards were on separate sites. Especially in urban hospitals there was concern that poor quality primary care contributed considerably to paediatric workload, through inappropriate referrals and telephone calls from parents who were unable to contact their general practitioner.

There were also a number of specific problems in individual units. For example, in one hospital, adult patients with thalassaemia or sickle cell disease continue to be treated by paediatric junior staff, undergoing check ups and transfusions in the evenings to fit in with their employment. It may take up to an hour to treat each patient, at a time when doctors are particularly busy with calls from accident and emergency departments. In another, a blood gas analyser was provided but without technical support. On occasions senior house officers spent up to two hours repairing it.

CONSENSUS PANEL

Two broad areas of concern emerged from the first phase attendance at deliveries and certain technical tasks. Tasks that clearly require a doctor (clerking and examining patients, prescribing drugs, talking to relatives and senior colleagues) were not considered by the panel and administrative and clerical tasks had been considered by another panel (to be reported elsewhere). This left two areas for discussion: technical tasks and attendance at deliveries.

TECHNICAL TASKS

Following discussion, the panel considered many of these tasks need not be performed by a doctor (table 4). Some panellists were initially reluctant to accept this view but agreed that nurses could take on such roles if they were properly trained. It was, however, pointed out by other panellists that many paediatric senior house officers receive no formal training in taking blood samples and

Table 4 Appropriateness of tasks being performed by someone other than a doctor

Task	*Level of agreement*	*Median score**
Must be done by doctor:		
Take arterial blood from child, no arterial line in situ	Agreement	1
Need not be done by doctor:		
Site an intravenous cannula in a child	Agreement	9
Site an intravenous cannula in a neonate	Partial agreement	8
Draw/make up intravenous drugs	Agreement	9
Administer intravenous drugs	Agreement	8
Take venous blood from a child	Agreement	9
Take venous blood from a neonate	Partial agreement	9
Do a heel stab on a neonate	Agreement	9
Take arterial blood from child or neonate with arterial line in situ	Agreement	9
Analyse blood samples in neonatal unit	Agreement	9
Disagreement:		
Take arterial blood from neonate, no arterial line in situ	Disagreement	
Intubate a neonate after delivery	Disagreement	

*Score: 1, must be done by a doctor, 9, can always be done by someone else.

inserting cannulae in children. One panellist contrasted this with a Canadian unit in which nurses are responsible for all intravenous infusions. It was also noted that when doctors are required to give intravenous drugs, other tasks such as attending deliveries take precedence and the drugs are often given several hours late. This would be avoided if they were given by nurses on drug rounds.

Panellists challenged the practice in some units for doctors to give the first dose of all routine intravenous drugs because of the possible risk of anaphylaxis. It was felt to be unnecessary as a reaction could occur at any stage in a course of treatment.

The inclusion of heel stabs in the discussion aroused surprise among those panellists working in units where it is a routine nursing task, although others reported that it is always done by doctors in their units.

The disagreement about intubating neonates partially reflected an ambiguity in the question. It may be required in two situations: as an emergency after delivery if a paediatrician is not present and if a tube becomes dislodged in a neonatal unit. In the first case it was argued that midwives should be able to intubate, although there was concern that they might lose their skills if they were not doing it routinely. Others argued that resuscitation with a bag and mask was often adequate until a paediatrician arrives.

Arterial stabs in neonates also produced disagreement. While some panellists took the view that nurses could perform the task satisfactorily, others disagreed because of the perceived risk of arterial spasm. However, it was argued that a nurse could manage this as well as a doctor. One panellist expressed caution that a policy whereby nurses could take samples only from arterial lines may lead to their more widespread use.

ATTENDANCE AT DELIVERIES

The panel's views on the need for a paediatrician to attend deliveries in particular circumstances are shown in table 5. The reasoning behind these views will be discussed for each situation in turn.

(1) PREGNANCIES 'AT RISK' FROM THE ANTENATAL HISTORY

Maternal diabetes

The question was restricted to an otherwise uncomplicated labour. Several arguments were advanced for a paediatrician being present, including the high incidence of unexpected congenital abnormalities, and the need for an additional pair of hands as the midwives and obstetricians may be involved with problems affecting the mother. The need for careful preparation was stressed, and several commented that they should be planned to match laboratory working hours. The lack of complete agreement partially reflected a dichotomy in which those working in London felt that a paediatrician should be present, whereas those outside London felt that it was only that the infant should be seen within one hour. Presence at such deliveries may have a lower priority than some other tasks.

Rhesus incompatibility

A paediatrician should be present if the baby is premature and anaemic but not if there has only been a rise in antibody during pregnancy. However, each case should be discussed between the obstetricians and paediatricians in advance.

Pre-eclampsia

These pregnancies will be monitored closely by obstetricians. The panel agreed that a paediatrician need only be present if the fetal heart trace was unsatisfactory or the baby has not been growing well.

Known congenital abnormality

This topic generated considerable debate. Many mild abnormalities would not require a paediatrician, although prenatal diagnosis is often uncertain and unforeseen problems may arise. Even when a paediatrician is not required at the delivery, the infant should be seen soon after. The paediatrician has a dual function in deliveries of infants with major abnormalities: resuscitating the infant and counselling parents. Such deliveries should be planned, and when

Table 5 Indications for a paediatrician to be present at a delivery

Indication	*Level of agreement*	*Median score**	*Need for paediatrician*
(1) Pregnancies at risk from the antenatal history:			
Maternal diabetes	Partial agreement	2	Sometimes
Rhesus incompatibility	Agreement	5	Sometimes
Pre-eclampsia	Agreement	5	Sometimes
Known congenital abnormality	Partial agreement	3	Sometimes
Multiple births	Agreement	1	Yes
(2) Preterm births (weeks' gestation):			
34–36	Agreement	5	Sometimes
30–34	Agreement	1	Yes
<30	Agreement	1	Yes
(3) Difficulties during labour:			
Abnormal presentation	Agreement	1	Yes
Suspected birth asphyxia	Agreement	1	Yes
Meconium staining	Agreement	4	Sometimes
(4) Instrumental deliveries:			
Lift out forceps	Partial agreement	6	Sometimes
Difficult forceps	Agreement	1	Yes
Emergency caesarean section	Agreement	1	Yes

*Score: 1, paediatrician must be present, 9, paediatrician need never be present.

appropriate, should take place in hospitals with a paediatric surgical unit. It is preferable for a consultant to counsel the parents, and this is likely to be unsatisfactory if done in the middle of the night. The final rating reflected the lack of specificity in the question. The topic requires more detailed consideration, and cases should be discussed individually between a paediatrician and an obstetrician.

(2) PRETERM BIRTHS
It was noted that junior staff in many hospitals are called to all preterm births. However, it was agreed that infants of 34 weeks' gestation or more rarely have problems, and as they are intensively monitored the need for a paediatrician can usually be predicted.

(3) DIFFICULTIES DURING LABOUR
A paediatrician should always be present in cases of abnormal presentation and where asphyxia is suspected from the fetal heart trace or fetal blood monitoring. It is especially important in the latter case because of the medicolegal implications. There was much more debate about the importance of meconium staining, with differing views about the correlation with asphyxia. It was noted to be a common reason for being called to a delivery, but many babies required no treatment.

(4) INSTRUMENTAL DELIVERIES
A paediatrician should be present for difficult forceps deliveries and caesarean sections, but there is less certainty about 'lift out' forceps deliveries. One panellist cited a hospital in which only one of two obstetric teams routinely called a paediatrician.

Discussion

During the past 30 years there have been major increases in the workload of paediatricians. General paediatrics has been affected by the steady increase in attendances at accident and emergency departments, and the ability to treat babies of ever decreasing gestation has increased the scale of neonatal care dramatically.[5] This has affected both the number of infants treated, and also the complexity and intensity of treatment. However, changes in the work pattern of doctors have not kept pace with these changes, with the result that paediatrics is generally recognised to be the busiest speciality in a typical hospital.

This panel has provided a basis for discussions on ways to reduce this workload. Responsibility for many technical tasks could be adopted by other professionals. This may be less of a problem in paediatrics than elsewhere as, especially in neonatal units, many nurses have undergone advanced training. Attendance at deliveries could also be reduced. Although most of the factors considered by the panel are regarded as indications to call a paediatrician in each of the study hospitals, it was apparent that many junior paediatricians questioned these policies. Many of their reservations are borne out by the panel. The view that a paediatrician need not be present at all at lift out forceps deliveries is consistent with the findings of one of the few studies in this area which found no difference in the proportion of infants requiring resuscitation in spontaneous vaginal deliveries compared with those where Neville-Barnes forceps were used.[6] There is a particular need for improved communication in advance between obstetricians and paediatricians, but the panel has drawn attention to areas requiring more research in neonatal practice, such as the poor predictive value of current methods of intrapartum monitoring and uncertainty about the importance of meconium staining.[7] Also the role of a paediatrician at the delivery of an infant with a known congenital abnormality, and the skills which are required, need further consideration.

Applying the panel's conclusions to the activities recorded by senior house officers in the diaries, and with certain assumptions, our best estimate is that approximately 25% of the events recorded in diaries could be avoided. This increases to 40% if activities after midnight are considered separately. Such a reduction would not resolve all of the problems of junior paediatricians, and many would still have an arduous job. The importance of implementing such measures was stressed by some of the panellists who commented on the difficulty of recruiting junior staff. Paediatricians up to senior registrar grade often work for most of the night when on call. The implications of the panel's conclusions resemble those proposed in response to a similar problem in Canada where there was understaffing in many units and reluctance to enter the speciality resulting from the heavy workload and long hours of work.[8] The heavy clinical load was also felt to compromise the educational objectives of paediatric training posts. The authors argued that the problem required not only an increase in neonatologists, but also a consideration of whether some of the tasks undertaken by neonatologists could be performed by other professionals. This paper is a contribution to that debate.

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Radiotherapy in paediatric practice

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Compared with adults, the number of children requiring radiotherapy each year is very small (of 3000 new patients treated annually at the Bristol Radiotherapy and Oncology Centre, 50 are children) but the treatment of a child may make greater demands on time and resources than an adult. There are important differences between adults and children that must be considered by the radiotherapist. The greatest of these lies in the child's potential for growth, development, reproduction, and longevity. Radiation induced tumours rarely occur earlier than 10 years from treatment: therefore children cured of cancer have ahead of them many years of life, carrying a steadily increasing risk of a second tumour as age advances. The late effects of radiotherapy in children have been well described by Shalet and others.[1]

Although nearly all childhood cancers are radiosensitive, radiotherapy is used sparingly in children because of these late effects. The dose required for cure is similar to that needed in adult tumours but it is frequently given in smaller fractions over a longer period in the hope of reducing late damage. Other differences relate to the child's size at the time of treatment as this can lead to practical problems of geometrical accuracy due to small field size.

Practical aspects of radiotherapy in children

A necessity of all radiotherapy is that the patient lies absolutely still and alone during treatment (usually 1–2 minutes). This may be hard for an adult but more so for a child. It is usually necessary to give sedation or a short acting general anaesthetic, such as ketamine, in children under 3 years of age. Coöperation without the need for sedation may be obtained from the slightly older child by giving an explanation at a level suitable to its understanding, with full explanation to its parents. A similar detailed explanation should be provided for the more mature child and its parents. In Bristol, a playleader has designed a colouring book for young children and a realistic picture book for those who are older to aid preparation for radiotherapy.

It is frequently necessary to make a Perspex mould for patients receiving localised treatment to the head and neck region. This necessitates a plaster of Paris model of the child's head to be made initially. A doll, complete with its own Perspex mask and a plentiful supply of plaster of Paris for the child to play with, often helps to reduce the stress of the situation. A playleader, experienced in such preparation, will ease the task of the radiographers who give the treatment. Many adolescents and adults would benefit from similar preparation.

RADIATION INDUCED VOMITING

Radiotherapy only causes vomiting when the abdomen, and particularly the upper abdomen, is in the radiation field. This is the case in total body irradiation, the treatment of Wilms' tumour and when treating the spine, if the radiation beam exits through the stomach. Where the daily fraction size is 200 cGy or less and the field size not large, vomiting is usually easily controlled and much less severe than that induced by chemotherapy.

Prochlorperazine (250 µg/kg every eight hours) is a useful drug which can be given orally or rectally. If this fails, oral metoclopramide or domperidone may prove successful. Where it is necessary to use parenteral drugs a regimen with alternating chlorpromazine (0·5 mg/kg intravenously) and promethazine (0·5 mg/kg intravenously) every four hours is useful, particularly in younger children; those who are older often dislike the sedation produced. As irradiation induced vomiting generally occurs within hours of the treatment, it should be possible to time the treatment and antiemesis so as not to interfere with nutrition and hydration.

Total body irradiation is the treatment most likely to induce vomiting, particularly when given as a single fraction. Fractionated therapy, however, will lead to some vomiting in about 50% of children receiving standard antiemetic drugs. When used in patients receiving fractionated total body irradiation the recently introduced $5HT_3$ receptor antagonist, ondansetron, abolished vomiting in 55% and reduced it to mild in a further 27% of cases (RF Stevens. Third International Congress on Neoadjuvant Chemotherapy, Paris 1991).

The changing role of radiotherapy in paediatric malignancy

The improved survival in leukaemia and in childhood solid tumours brought about by the advent of more effective chemotherapy regimens[2] has made clinicians aware of the need to minimise the late sequelae of treatment.[3] This has led to a change in the role of radiotherapy in the management of some paediatric tumours. It remains the mainstay of treatment for brain tumours, after neurosurgery in most instances, and its emergency use in children presenting with superior vena caval obstruction or respiratory embarrassment from mediastinal lymphomas continues to be important.

The use of radiotherapy in bone tumours has lessened. Completely resectable tumours are treated with surgery and chemotherapy alone. It still has an important part to play, however, in Ewing's sarcoma where the tumour is at a site inaccessible to surgery, where there is residual disease after surgery, and by its preoperative use in large primary tumours to make them resectable.

Studies are being undertaken to define the precise part radiotherapy plays in the management of a number of other tumours. Attempts to refine its use are well illustrated by considering Wilms' tumour, acute lymphoblastic leukaemia, and rhabdomyosarcoma.

WILMS' TUMOURS

Eighty per cent of UK patients are registered with the United Kingdom Children's Cancer Study Group (UKCCSG) Wilms' tumour studies. The aims of the second such study include continuing refinement of therapy 'in the hope of further reducing side effects without compromising efficacy' (UKCCSG. Second Wilms' tumour study, June 1986). It has been shown that study patients have increased survival with decreased treatment sequelae.[4] Serial studies have allowed a reduction in the number of patients receiving radiation. Patients in stage I or II (tumour completely excised) in the UKCCSG second Wilms' tumour study receive no abdominal irradiation. Patients in stage III (residual non-haematogenous tumour confined to the abdomen) with operable disease and favourable histology, receive a dose given to the abdomen which is lower than the dose given to those with initially inoperable stage III disease or unfavourable histology. Thus fewer children with Wilms' tumours are receiving irradiation than prevously; of those who do, some receive a lower dose.

ACUTE LYMPHOBLASTIC LEUKAEMIA

In the next Medical Research Council trial for acute lymphoblastic leukaemia, cranial irradiation will be omitted in those children whose presenting white cell count is less than $50\times10^9/l$; cranial prophylaxis will be achieved by regular intrathecal methotrexate with or without high dose systemic methotrexate. Those whose presenting cell count is greater than $50\times10^9/l$ will be randomised to receive cranial irradiation with standard intrathecal methotrexate or both systemic and intrathecal methotrexate. It is hoped these changes will reduce late sequelae such as learning problems and abnormalities of growth and puberty, probably attributable to cranial irradiation.[5]

RHABDOMYOSARCOMA

Refinement in the treatment for rhabdomyosarcoma in childhood is directed towards improving the quality of life of cured children by reducing late sequelae, many of which are due to the effects of irradiation on developing tissues. Based on results of previous rhabdomyosarcoma studies, stage I patients (those with complete resection of tumour) no longer receive radiotherapy. In current International Society of Paediatric Oncology studies of disease in nonparameningeal sites, radiotherapy is confined to those patients who do not have a complete response to chemotherapy with or without surgery. Using these criteria there will be a greater number of relapses but only those who relapse will receive radiotherapy as part of their salvage management, thus avoiding irradiating many patients.

Palliation

Despite advances in the management of paediatric malignancies, 30–40% of such children diagnosed will die of their disease. For some of these patients palliative radiotherapy plays a part in symptom control. In a recent study from Bristol, of terminal care in children, 40% received palliative radiotherapy during the terminal phase of their illness.[6] This is many more than in the study reported from the Hospital for Sick Children, Great Ormond Street, where only 9% received radiotherapy.[7] This may reflect a different spectrum of tumours studied or the ease of access to a radiotherapy department. The children in our study all lived within a 25 mile radius of the hospital where the terminal care team worked, whereas 56% of children in the second study lived greater than 20 miles from the treating hospital.

The aim of palliative treatment is to obtain rapid relief of symptoms using the smallest number of radiotherapy fractions compatible with the desired response and with as few side effects as possible. A team approach to terminal care should include ready access to a consultant radiotherapist with a special interest in paediatrics. The need to travel long distances, combined with referral to a radiotherapist unfamiliar to the family, may contribute to a lower use of radiotherapy than is desirable.

The commonest indication for palliative radiotherapy in children is pain: others include control of primary tumour masses in the presence of untreatable metastatic disease, treatment of lymph node masses causing pain and/or oedema, and control of neurological symptoms. Dose and fractionation depend on site, tumour type, and precise cause of pain.

Limb pain caused by bone marrow infiltration from leukaemia or neuroblastoma, and less frequently by localised bony metastases, can be treated with a single fraction of radiotherapy.[8] Pain relief usually occurs within hours of treatment and is likely to be achieved within a week. Local or systemic upset from this kind of treatment is extremely uncommon.

Metastatic lymph node masses may cause pain and oedema; treatment of these can be completed in 10 days using three to four fractions. Improvement will occur within a week of starting treatment and will be maximal at two to three weeks. Local side effects should not be severe but mucositis may be troublesome if it is not possible to exclude the mucous membranes from the irradiation field. Erythema may occur after radiation, particularly in skin folds such as the groin, but is unusual in palliation.

Greater systemic upset is expected when treating the trunk. Symptoms due to mediastinal lymph nodes can be relieved by radiotherapy, and the progress of lung metastases from some tumours, such as osteosarcoma, may be controlled for many months by whole lung irradiation. When treating large volumes of the trunk, it is usually necessary to fractionate treatment over at least five treatments to the mediastinum and 10 to the whole lung. Dysphagia occurs in most patients where the oesophagus is in the field. It is temporary and can be relieved by preparations such as oxethazaine. Short term general malaise and tiredness often follows the treatment of large volumes by radiotherapy and it may be difficult to distinguish these from the disease process. If radiation pneumonitis occurs, it will cause shortness of breath three weeks to three months after radiation. Symptomatic relief is obtained with a short course of steroids, typically prednisolone 40 mg/m^2 per day.

One of the commonest reasons for palliative irradiation of the abdomen is painful recurrent abdominal neuroblastoma. The principles of treatment and side effects are similar to those for chest irradiation, though vomiting maybe more severe. Diarrhoea is common but is likely to be mild and responds to symptomatic treatment. The pain relief achieved is often prompt and justifies the temporary side effects of the radiation. Upper or lower half body irradiation is a very useful way of palliating children with very widespread painful metastases.

Cranial irradiation for recurrent brain tumours or brain metastases is well tolerated and frequently allows a reduction in dexamethasone dosage. However, it causes alopecia and, as life expectancy is often short, it is particularly poignant that parents may comment that worthwhile regrowth of hair is only obvious at about the time of dying. Emergency irradiation may be given for spinal cord compression: a fractionated course of 5–10 treatments will usually be necessary. Benefit, with good pain relief and improved function, can be achieved but established neurological deficit is unlikely to be reversed.

Conclusion

Radiotherapy has an important part to play in the management of some paediatric tumours. A team approach, with paediatric oncologist working in close association with radiotherapist, paediatric surgeon, paediatric pathologist, and radiologist is necessary for optimal care of children with cancer.

Treatment should ideally be carried out in centres where at least one radiotherapist, familiar with national and international protocols, takes special responsibility for children in order that sufficient experience may be obtained in managing these rare conditions. In the event of treatment failure, close liaison allows quick and effective palliation to be carried out. Adolescents and young adults requiring multimodal therapy would also benefit from such an approach as cancer management becomes more complex.

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PERSONAL PRACTICE

Quality assurance in the emergency room

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Quality assurance programmes have become an accepted part of health care delivery in hospitals in a number of countries. In addition to their value as management and clerical systems designed to ensure that clinical care is of an acceptable standard,[1] they have also become popular among administrators who see the implementations of quality assurance programmes as a measure of the efficient and effective allocation and use of resources.[2]

There are three general approaches to the development of quality assurance progammes[3]: (a) structural approaches—for example, addressing issues such as medical education, practitioner training and registration, equipment and facilities, (b) evaluation of the outcomes of health delivery, and (c) documenting and assessing the process of delivering health care.

Most studies of quality assurance in clinical medicine have focused particularly on process and outcome as an index of the quality of care.[4] For example many existing programmes study such parameters as the adequacy of medical records, patient satisfaction, laboratory utilisation, waiting times, and outcome variables such as mortality, postoperative infection or complication rates, duration and severity of symptoms, and so on.[5] There have been criticisms of both these approaches. Outcomes are not always easy to measure, and especially in the case of paediatric practice outcomes are not always attributable directly to the care provided[6 7]: for example children with viral upper respiratory infections are likely to get better irrespective of what type of care they receive. An evaluation of the process of care is usually a judgment rather than a precise objective measurement.[8] Furthermore, interventions designed to improve the process of health care may not always be congruent with the priority outcome goal of improved health status. For example though it is desirable to decrease patient waiting times, admission rates, and the number of laboratory investigations performed, there comes a point when the pursuit of these process goals may be counterproductive in the context of improving health outcome. Reducing the waiting time should not be at the expense of an unhurried, thorough evaluation of each patient. Nevertheless, despite these shortcomings these approaches generally do provide a means of holding health care providers accountable for following procedures that are, to the best of current knowledge, appropriate and optimal.

The maintenance of high standards of clinical care in paediatric emergency rooms poses particular challenges. These include:

- The high patient attendances, so that doctors and nurses frequently work under considerable pressure to see patients quickly
- The uneven nature of the workload
- The tendency for the emergency room to be staffed by junior staff with relatively little experience
- The rotation of doctors through the emergency room for limited periods of time, and the need for rosters covering the whole 24 hour period, thereby limiting their exposure to and reducing the potential effectiveness of educational activities
- The life threatening nature of many of the presenting conditions.

It is not surprising that quality of care questions are perceived as the least of the problems facing emergency room directors and administrators, and may explain the relative paucity of articles and studies focusing on quality assurance in this setting.[7 9–14] However, one could argue that it is *because* of the difficulties outlined above that emergency quality assurance measures are especially important.

In this paper we describe a programme of such measures developed for the emergency room of a large paediatric teaching hospital. We focus in particular on the structural and process areas of quality assurance and argue that while individually simple and inexpensive to introduce, together they provide a framework for facilitating the delivery of quality clinical care in a paediatric emergency setting.

Background

The Royal Children's Hospital, Melbourne, is a large, freestanding paediatric teaching hospital which provides the full range of primary, secondary, and tertiary services. Over 70 000 children per year are seen in the emergency room—about 40% of these are triaged to an adjacent walk in clinic within the department (general clinic). At any one time, 16–18 doctors in their second and third year postgraduation work varying rosters to cover the department on a 24 hour basis. Approximately 60 residents rotate through the department each year. The majority of these are not paediatric trainees but rotate from other hospitals and family practice training programmes for three months of paediatric experience. When they arrive in the department the vast majority have had no prior paediatric experience.

In addition a number of registrars (doctors who are in their second to sixth year of paediatric training) are rostered to emergency to provide supervision for the residents and assess children for admission; there are two registrars from 0900–2300 hours and one registrar during the night. The residents work a variable roster with approximately 60% of their time spent in emergency and the remainder in the general clinic, to which children with less acute/severe conditions are triaged. From 0900–2300, when the general clinic is operational, only children with acute/severe conditions, babies aged less than 1 month, or those presenting because of trauma, are seen in the emergency room. Outside these hours all patients are seen in the emergency room. Because of the range of services provided by the hospital many children present with manifestations of serious tertiary diseases such as congenital heart disease, cystic fibrosis, or metabolic disease. Just over 10% of all patients seen in the emergency room are admitted, with a further 18% reviewed either by telephone or in person by departmental staff. The source of referral of all patients is seen in the figure. Four consultant paediatricians work in the department, and although each has extensive responsibilities in other areas, one is available on an on call basis for the emergency room.

This emergency room thus encompasses many of the quality assurance challenges previously mentioned: a large volume of patients many of whom are very sick, inexperienced doctors who change every three months, and variable rosters which make the planning of educational activities difficult.

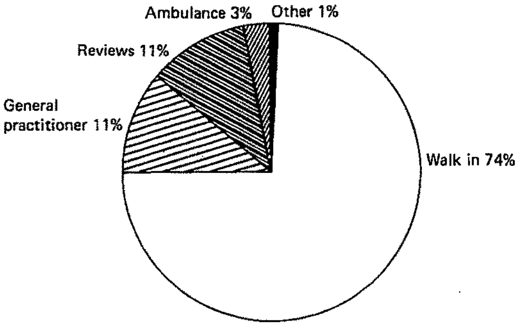
Conceptual framework

Several concepts permeated the evolution of various programmes within the department and are reflected in some of the quality assurance measures. Firstly was the concept that the quality of care delivered in the emergency room had to reflect the standards of the hospital as a whole and its individual departments. For example the competence with which children with fractures and other orthopaedic problems were managed in the emergency room should be the equal of the way they were managed in the orthopaedic department. This meant negotiating with individual departments around the hospital for them to share responsiblity for the delivery of care in the emergency room by being involved on a equal basis in the development of clinical protocols and providing a 24 hour on call consultation service to the emergency room.

Secondly a conscious decision was taken that this would not be a 'freestanding' emergency room which operated in a quasi-independent fashion from the rest of the hospital. It was felt that it was unlikely that emergency room staff would ever develop the expertise of, for example, a surgeon or an intensivist. Rather than 'work up' the patient until a diagnosis was firmly established, and initiate investigation and management procedures, it was considered more efficient to request specialty registrars and consultants to be involved in the assessment of these patients in the emergency room at an early stage. If a child with multiple trauma arrived in the emergency room personnel from the inpatient services would be involved with the patients as soon as possible after arrival. This meant that each hospital department gave a clear message to registrars and consultants that consultation to the emergency room was a high priority.

Thirdly the department had a commitment to the health of the children of the whole community, not just those who sought care at the hospital. For example written and oral communication with family doctors was considered important, and this added to the time the doctor spent with each patient. Furthermore the obvious advantage in employing only those residents committed to a full year in paediatric training had to be balanced by our desire to offer paediatric experience to as many family practice trainees as possible.

This conceptual framework guided and influenced the development of the quality assurance programme in the emergency room.



Source of referral.

Components of the programme

The individual components of the quality assurance programme are outlined in table 1 and will be detailed below.

ORIENTATION/EDUCATION

It is clearly impossible for doctors to deliver quality care if they are unfamiliar with institutional and departmental policies and procedures or if they have an insecure knowledge basis in paediatrics. A great deal of effort is put into orientation and education.

Orientation

Detailed written orientation guidelines are sent to each resident before commencement—this covers rosters, organisational structures, logistics, teaching and supervision, and other details of their service in the department. On the morning of commencement a two hour long group orientation is conducted by department staff, followed by individual orientations to the emergency room and general clinic. During the subsequent two weeks there are informal personal follow up meetings with each resident to

Table 1 Individual components of the quality assurance programme

(A) Orientation/education
- (1) Orientation for new residents:
  - Written orientation guidelines
  - Group orientation
  - Individual orientation
- (2) Education:
  - Primary care training programme in paediatrics (with family medicine programme of Royal Australian College of General Practitioners)
  - Library of videos, tape slide programmes, textbooks, individual articles/book chapters
  - Weekly lunchtime case presentations
  - Daily radiology reviews
- (3) Written protocols:
  - Clinical protocols for many conditions
  - Parent handouts to aid explanation

(B) Supervision/consultation
- (1) Supervision by registrars in department for 24 hours
- (2) Departmental consultant on call for 24 hours
- (3) Consultant paediatrician in general clinic
- (4) Inpatient service registrars on call for 24 hours—for example, orthopaedics, intensive care, surgery, plastic surgery, etc
- (5) Specialty/resident review clinics: dermatology, ear, nose, and throat, speech pathology, developmental screening programme, behaviour clinic

(C) Data collection
- (1) Detailed data collection system—demographics, patient details, resident work profiles, etc
- (2) Injury surveillance

(D) Process review
- (1) Chart review—formal and informal
- (2) Monitoring of patient waiting time
- (3) Review of investigations:
  - Radiograph report feedback form
  - Daily radiology review meetings
  - Review of all laboratory results—haematology, biochemistry, bacteriology
- (4) Patient review:
  - Appointment
  - Telephone
- (5) Participation in hospital practice review
- (6) Referred patients—registrar or consultant review
- (7) Review of patient admissions

(E) Others
- (1) Patient complaints
- (2) Formal communication mechanisms:
  - (a) Internal—staff meeting, communication book
  - (b) External—letters to family doctors, family doctor meetings, 'business section'

ensure familiarity and comfort within the department.

Education

In addition to the informal teaching that is part and parcel of most health care systems a number of more structured activities have been organised. A formal curriculum in primary care paediatrics was developed some years ago in conjunction with the family medicine programme of the Royal Australian College of General Practitioners. It consists of 57 one hour tutorials which cover in theory what a practising family doctor needs to know to be reasonably competent in paediatrics; teaching sessions are held each afternoon. Weekly lunchtime case presentations take place, run by one of the consultants, in which residents present and discuss interesting cases seen in the previous week.

Each weekday a radiologist reviews with the group of residents radiographs taken the previous day. An extensive library of textbooks, videos, tape slide programmes, and selected articles and book chapters is kept in the department and used extensively by residents.

Written protocols

Clinical protocols have been developed for approximately 50 conditions and are utilised as departmental guidelines for the management of these conditions. As previously mentioned, most protocols are developed as a joint effort between staff of the department and from the relevant specialty department, for example, gastroenterology and orthopaedics.

To ensure some consistency in the information presented to parents, parent handouts have been developed for many common paediatric conditions (currently 15). They are written at an 11 year old reading level on brightly coloured paper and are given to parents to taken home after their emergency room attendance. These are being distributed to health professionals throughout Australia.

SUPERVISION/CONSULTATION

Because most doctors working in emergency rooms are relatively junior and inexperienced, supervision and the availability of around the clock consultation are mandatory. Registrar supervision is provided in the emergency room on a continual basis and a departmental consultant is also available. The consultant is on site during normal working hours and then on call after hours and on weekends. In this sense our department probably differs little from others. However, there are three other levels of supervision and consultation which are innovative.

(1) Inpatient service registrars

As previously mentioned registrars and consultants from the various inpatient services provide a continuous on call service to the emergency room. Most children with fractures, for example, are reviewed by an orthopaedic registrar before any decision about definitive management. A child with epiglottitis or severe croup, or other life threatening illness, is seen immediately by a registrar or consultant from the intensive care unit. Surgical registrars consult with emergency staff for children with abdominal pain, soft tissue trauma, and so on. There are several benefits of this system: the child receives more expert care and decisions made about diagnosis and treatment are more likely to be appropriate. Unnecessary admissions to hospital are more likely to be avoided and the process of consultation provides important learning experiences for staff of the emergency room.

(2) Consultant paediatrician in general clinic

This has been described previously.[15] For a number of years consultant paediatricians have been transferred from the outpatient department to the general clinic where they teach and supervise residents. Definitive expertise is provided at the point of first contact for the patient. Many children who would have been referred to outpatients are now effectively managed in the general clinic, usually at the initial visit, and returned for ongoing care to their family doctor. The implications for teaching, role modelling, and quality assurance of having an experienced paediatrician working alongside resident doctors are obvious. After hours this service is provided by senior paediatric fellows working in the general clinic. Although these fellows see patients independently, they also are available for consultation with residents.

(3) Specialty/resident reviews clinics

The principle espoused above of providing definitive consultation in the walk-in clinic rather than an isolated outpatient department was extended to a number of specialties in addition to general paediatrics. Specialist consultant clinics are held regularly for dermatology, ear, nose, and throat, speech pathology, developmental screening, and behaviour problems. Rather than referring a child to the outpatient department the resident arranges for the child to return on one of the specialty clinic days where the designated specialist is available in the general clinic to consult with them. The advantages for teaching, patient and doctor convenience, hospital efficiency, and quality assurance are clear and it is planned to extend this system further.

DATA COLLECTION

The collection of data is an essential prerequisite to programme evaluation as without the provision of a continuous and reliable data set the provision of efficient services of a high quality is made very difficult. In addition to the usual demographic data (age of child, time of arrival, diagnosis, disposition) information is also collected about consultation, investigations, and complexity of the illness, and data can be analysed individually for all residents (see table 2). We are thus able to build up a 'practice profile' for each doctor. This profile includes how many patients are seen, their diagnoses, how often a consultation with a senior doctor is obtained, how many laboratory investigations are performed and in which context, what proportion of patients are reviewed or referred to outpatients, and so on. This is a valuable teaching aid in that we are able to describe a resident's paediatric experience and identify possible gaps in training. Its use as a quality assurance measure is even more valuable because we can document 'outliers' from average practice. For example if we find a resident bringing back patients for review twice as frequently as his/her colleagues or performing an unusually high proportion of laboratory investigations, this will point to the need for that resident's practice to be reviewed as it may be an indication of lack of expertise or confidence. Other similar analyses can be performed in the interests of delivery of high quality paediatric care.

Table 2 Prospective data collection in the emergency room

Patient identification number
Date of birth
Sex
Residential postal code
Source of referral (for example, walk in, family doctor, etc)
Time of arrival
Time of consultation
Resident identification number
Diagnosis (abbreviated codes from ICD-9*)
'Severity' of disorder
Consultation (for example, emergency room registrar, consultant)
Laboratory investigations (for example, haematology, biochemistry, blood/urine/cerebrospinal fluid cultures, etc)
Procedures (for example, venepuncture, lumbar puncture, etc)
Time of discharge from department
Disposition (for example, home, no follow up, patient review, phone review, review by local doctor, outpatient referral, etc)

*ICD-9, *International Classification of Diseases*, 9th revision.

PROCESS REVIEW

A series of reviews of the *process* of delivery of care takes place in a number of areas. There are formal and informal chart reviews—each morning the consultant conducts a chart review session with the resident and registrar who have worked the night roster. Informal ad hoc chart reviews are conducted by registrars and consultants on a continual basis.

Similarly, laboratory investigations are reviewed on a formal basis. In addition to daily radiology review meetings residents are given rapid feedback about their interpretation of radiographs by use of the 'radiograph report feedback form' previously described.[16] These forms are initially returned to the paediatrician responsible for emergency so that he can act on any radiographs that have been interpreted incorrectly by the resident. Sometimes the misinterpretation is of little consequence but at other times it has significant implications for patient management. All laboratory investigations are entered into a central log book and results reviewed formally each day by a 'designated resident'. It is his/her responsibilty to telephone parents with results and change or initiate appropriate treatment. This provides a 'safety net' process that ensures that significant laboratory results (particularly microbiology cultures) are always acted upon.

All patient reviews by residents are centralised in a single appointment book so that they can be monitored. Patient waiting time is monitored and times that exceed predetermined levels are acted upon by the consultant. All patients referred by practitioners in the community are formally reviewed by a consultant or registrar before decisions about disposition, and a consultant sees each chid who is being considered for admission. Finally patients seen in the emergency room are included in those discussed at the formal hospital practice review meetings.[17]

OTHERS

There are several other items which are included in the department's quality assurance programme. Patient complaints are acted upon formally, documented, and procedures reviewed in an attempt to address any underlying problems that led to the reason for the complaint. Complaints are often used as the basis for weekly resident case discussions. Finally, communication both within the department and with the community is taken seriously. Written and telephone contact with family doctors are encouraged, and a summary letter form has been introduced to facilitate this. At regular bimonthly educational meetings of family doctors at the hospital, a 15 minute 'business section' is conducted where community doctors provide feedback to us about patient care, follow up, discharge letters, and a host of other issues.

Within the department, apart from regular formal staff meetings, there are communication books where staff include information about incidents and problems; these are acted upon the next day by senior staff.

Discussion

It has been argued that quality assurance is a process, never an event.[18] We have attempted to develop quality assurance measures as an underlying philosophy of delivering health care. Given the realities that face us and many other emergency rooms—rotating, inexperienced residents dealing with large numbers of often very ill patients—it was essential for us to provide a 'safety net' of the described measure in an attempt to facilitate quality services.

Some may argue that many common, acute ambulatory problems will resolve themselves satisfactorily whether or not there has been any medical intervention and whether or not that intervention has been appropriate. This might be one of the reasons there are so few reports of quality assurance measures in emergency rooms or in other ambulatory settings.[17] Indeed most attention has been focused traditionally on inpatient services. In some instances these have been focused on outcome (for example, surgical complications, deaths) but more often it is the process of care examined. In many conditions it is difficult to focus on quality of outcome because of difficulties in accurately measuring changes in a patient's condition, let alone in attributing any changes to the specific intervention.[1]

Our programmes focus particularly on the structure and process of delivering care. Given 16 new residents every three months, as well as a high turnover of rotating registrars, we try to ensure from the outset that quality of clinical care is not compromised by a resident's unfamiliarity with the policies, procedures, and logistics of a new department. The orientation programme is time consuming for everybody involved and is compulsory for all residents, irrespective of their particular shift. Formal evaluations at the completion of resident terms indicate that the orientation has been found to be very valuable. Similarly, the availability of specific clinical protocols provides a structure from the outset for the delivery of consistent, high quality clinical care.

We believe that the level and range of consultation and supervision greatly enhances both teaching and patient care. Ambulatory care at the hospital has been rethought to address the principle of specialist consultant care to be provided to the patient at the point of first contact with the hospital wherever possible. Previously residents would refer children to an outpatient clinic, often weeks or even months away, and meanwhile be uncertain about diagnosis and management. Paediatricians are now available during normal working hours to provide immediate consultation so that a much higher level of expertise is provided. This greatly enhances teaching and significantly improves the quality of care. This aspect of the department consistently receives the highest ratings in resident evaluations of their term in ambulatory paediatrics. It has been suggested that scheduling consultants to work in walk-in clinics in preference to the outpatient department is a far more efficient way to organise services at a hospital level, especially as the majority of referrals to outpatients come from walk-in patients rather than from the community.[15] The contribution of such an arrangement to quality assurance is a valuable additional benefit.

Although long waiting times are an often accepted feature of hospital emergency rooms because of the imbalance between staff and patient numbers,[19] and the uneven and unpredictable attendances, it does not necessarily follow that the amount of time residents spend with patients has a major influence on the quality of care received. The availability of appropriate and immediate supervision will greatly facilitate productivity because residents spend less time with assessments, perform fewer unnecessary investigations, and feel more decisive about management. However of great importance also is a data collection system that allows us to develop profiles of resident work. This allows the early identification of those who require more guidance or counselling. With over 60 residents per year it is inevitable there will be a wide range of competence and confidence. The early flagging of those who work differently from their peers allows appropriate interventions to take place and is a major component of our quality assurance measures.

A number of the process reviews that have been implemented are innovative, such as the radiograph report feedback form.[16] It is in this area that we continue to evolve mechanisms for monitoring the quality of our clinical care. It could be argued that, with some exceptions,[15 17] the components of these quality assurance mechanisms are qualitative. There are few data to validate their effectiveness. The more difficult next step, notwithstanding the problems previously described, is to evaluate these measures in a quantitative manner against specified outcome criteria. However in an area where reported quality assurance measures are sparse, we have developed a comprehensive series of strategies and processes which greatly increases the likelihood of our providing consistent quality care to children and their families.

Not all components of the quality assurance programme described in this paper are relevant to all emergency rooms. In many hospitals there may be financial, logistic, or political constraints which preclude the introduction of such measures even if they are seen as relevant and desirable. Paediatricians who have involvement with the emergency rooms of general district or community hospitals, for example, may have difficulty providing as much senior level supervision of junior staff as they may wish, or in implementing comprehensive teaching programmes. Nevertheless, the broad concepts of quality assurance are relevant to all and certain key components of our quality assurance programme can probably be applied in most settings.

Accurate, prospective collection of data is clearly critical to any quality assurance undertaking. Unless emergency rooms have reliable data on patient numbers and characteristics, the types of medical conditions which present, and the way these conditions are dealt with, many aspects of the department's functioning will lack direction. Standard written protocols which provide a uniformity of approach to common clinical problems are even more important when direct supervision/consultation is not available. Formal staff orientation procedures and access to educational materials are also measures within the capability of most small hospitals.

Paediatricians face the challenge of selecting the quality assurance options most appropriate to the needs of their own hospitals and the population of children and families they serve.

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LETTERS TO THE EDITOR

Survival and place of treatment after premature delivery

Sir,—Dr Field *et al* are not justified in concluding from the data presented that there should be a more centralised service for babies of 28 weeks' gestation or less.[1] They found that babies of 28 weeks' gestation or less treated in large centres had higher survival rates than those treated in smaller units. It is likely that this is due to selection in the smaller units of appropriate babies to refer to the large centres.

Data from our unit, which is in the Trent region, were included in the report. We have a policy of transferring babies of 28 weeks' gestation or less to a regional centre. Two categories of babies are not transferred: firstly babies who are so ill that they do not survive long enough to be transferred or are not likely to survive transfer, and secondly babies who are considered previable. During the time of the study, three babies of 28 weeks' gestation or less were not referred from our unit to a large centre, but remained in our unit for terminal care. These were a second twin of 26 weeks' gestation with severe birth asphyxia and asystole at birth who died at 1 hour 20 minutes after unsuccessful resuscitation attempts, an infant of 24 weeks' gestation, and an infant of 21 weeks' gestation.

During the same period we referred postnatally 12 babies of 28 weeks' gestation or less to a large centre for neonatal intensive care. Four of these babies died. Clearly the difference in outcome for these two groups of babies is due to selection bias.

It is likely that similar decisions were taken in other smaller units in the region and comparison of survival in the two types of units is therefore not valid.

We believe that it is in the interest of selected very immature babies in our unit that we should transfer them to a large neonatal centre for intensive care. The results of this policy will be that those infants of 28 weeks' gestation or less who we do not transfer may well be receiving terminal care in our unit. It must not be concluded that these babies would have had a better chance of survival or better care had they been transferred to a large centre.

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1 Field D, Hodges S, Mason E, Burton P. Survival and place of treatment after premature delivery. *Arch Dis Child* 1991;**66**:408–11.

Dr Field and colleagues comment:
We thank Dr Salfield and his colleagues for their comments. Clearly we were concerned that small neonatal units might retain an excess of babies who were considered to have little chance of survival. It was for this reason we employed a method of disease severity scoring.[1] This approach (as reported in the paper) did not indicate that the group of babies treated in small units were at greater risk of death. However more sophisticated methods of disease severity scoring are now being developed and these should allow this finding to be confirmed. In addition it will then be appropriate to look at mortality in other gestation groups after correction for disease severity.

1 Patterson CC, Halliday HL. Prediction of outcome after delivery for the very low birthweight (<1500 g) infant. *Paediatric and Perinatal Epidemiology* 1982;2:221–8.

Birthweight ratio

Sir,—In our five centre study of 429 infants under 31 weeks' gestation, birthweight ratio was strongly related to requirement for ventilation, postneonatal mortality and anthropometry at 18 months, and largely unrelated to neurodevelopmental outcome.[1] Birthweight ratio, defined as birth weight divided by the mean reference birth weight for gestation, was proposed as a more useful outcome guide than growth retardation defined using an arbitrary cut off of the 3rd or 10th birthweight centile.

Recently, Brownlee and coworkers reexamined this concept in 436 infants from Leeds and claimed major discrepancies with our observations.[2] However, the authors agreed with our findings on the lack of relationship with neurodevelopmental scores (we found only a small deficit in language at 18 months), though neither study examined the prognostic value of birthweight ratio in more mature preterm infants. Brownlee and coworkers did not re-examine our data on long term growth and would not have been able to relate realistically birthweight ratio to postneonatal mortality as in their study the latter was so low.

Thus the only real area of conflict was over the relationship between birthweight ratio and need for ventilation. We found a strong linear trend—the smallest babies at any gestation requiring most ventilation. The Leeds study did not confirm this. We considered this might have been due to a secular trend in neonatal care since our cohort was recruited prior to that in Leeds. Therefore we elected to retest our findings on a new cohort of 231 babies below 31 weeks' gestation that were recruited during 1989–91 into a dietary study in two of our five previous centres. Using birthweight ratio and days of ventilation as continuous variables, and adjusting for gestation, there was a highly significant fall in duration of ventilation with increasing birthweight ratio, corresponding to an average of over seven days' reduction as birthweight ratio climbed from 0·7 to 1·2 (p=0·002). Using the same cut off values for ventilatory duration employed by us and by the Leeds group, of more than 7, 14, or 28 days the significance values for reduced ventilatory requirement with increasing birthweight ratio were 0·06, 0·001, and 0·009 (after adjusting for gestation), despite the smaller sample than in our previous study. We were, however, no longer able to confirm that growth retarded babies were more likely to need ventilation in the first 24 hours. Thus, apart from this, our two centre study reaffirms the results of the previous five centre one.

Possibly some aspect of respiratory management in Leeds accounts for the differences observed; we understand, for instance, that in Leeds ventilated babies are often paralysed, a procedure which was relatively uncommon in the five centres we investigated. We accept that studies on more centres would be valuable. Nevertheless, our own data, now based on a substantial cohort, have not led us to change our view on the clinical value of birthweight ratio.

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1 Morley R, Brooke OG, Cole TJ, Powell R, Lucas A. Birthweight ratio and outcome in preterm infants. *Arch Dis Child* 1990;**65**:30–4.
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Atrial natriuretic peptide and blood volume during red cell transfusion in preterm infants

Sir,—Rascher *et al* conclude that a slow transfusion of less than 10 ml red cells/kg body weight does not cause volume expansion.[11] Their plasma volume measurements are derived by subtracting the red cell mass from the total blood volume. The total blood volume was estimated from the red cell mass divided by the packed cell volume. The accuracy of the plasma volume estimations is obviously not only dependent on the accuracy of the red cell mass measurements but also on the accuracy of the packed cell volume measurements. The authors state that in adults whole blood packed cell volume is usually calculated by multiplication of the measured venous packed cell volume by 0·9. In preterm infants the authors agree the whole body: venous packed cell volume may also vary but do not correct for this. The published conversion factor for neonates is in fact 0·87.[2, 3] Furthermore the measurement of packed cell volume is liable to further error due to trapping of plasma between red cells which is dependent on the flexibility of the red cells. Even a mechanised system, such as a Coulter counter, for measuring packed cell volume by deriving a value from the mean corpuscular volume and red cell count is subject to error.

The method used to measure red cell mass is as described by Phillips *et al*,[4] which depends upon the dilution of fetal haemoglobin by an infusion of adult haemoglobin. The magnitude of the resulting changes in concentrations of fetal haemoglobin is not specified in either work, although the coefficient of variation of the actual assay technique for measuring fetal haemoglobin is stated to be <3·6%.[3] One wonders how accurately the small changes in concentration of fetal haemoglobin can be measured.

The study of Rascher and colleagues would have been more reliable if direct measurements of red cell mass and plasma volume had been made independently of each other. As the study stands the estimation of red cell mass is open to question and the measurement of plasma volume is flawed. A simple measurement of a change in the packed cell volume would have been as informative as the calculated changes in derived plasma volumes.

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1 Rascher W, Lingens N, Linderkamp O. Atrial

natriuretic peptide and blood volume during red cell transfusion in preterm infants. *Arch Dis Child* 1991;66:395–7.

2 Mollison PL, Veall N, Cutbush M. Red cell and plasma volume in newborn infants. *Arch Dis Child* 1950;25:242–53.

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4 Phillips HM, Abdel-Moiz A, Jones JG, *et al*. Determination of red-cell mass in assessment and management of anaemia in babies needing blood transfusion. *Lancet* 1986;i:882–4.

Drs Rascher and Linderkamp comment:

Dr Anthony and Professor Levene have raised important questions concerning the blood volume method used in our study. They point to the following possible pitfalls: (1) the method of red cell mass measurement may not be reliable. We used a method described by Phillips *et al* (that is, dilution of fetal haemoglobin by transfused adult red blood cells).[1] Phillips *et al* report a maximum coefficient of variation of less than 3·6%.[1] In 20 double measurements of fetal haemoglobin we found a mean variability (V= [A–B]/[A+B]/2) of 3·4%. This variability may have caused a mean error of a single red cell mass determination of 7%. This is in the range of other red cell mass methods.[2 3] The variability of fetal haemoglobin measurement and thus the error of red cell mass increases with decreasing fetal haemoglobin. (2) the microfuge packed cell volume has to be corrected for trapped plasma. Trapped plasma is about 2% for neonatal and adult red cells[4] and can thus be neglected. (3) the whole body packed cell volume differs from the venous (central) packed cell volume. In adults, the body: venous packed cell volume ratio is about 0·91. In full term neonates ratios of 0·87[5] and 0·90[2] have been reported, and in severely ill preterm infants ratios of 0·82 to 0·89 have been determined.[3] The use of a mean body:venous packed cell volume ratio derived from another study merely changes the blood volumes by a constant factor. The maximum error for blood volume calculation from red cell mass and packed cell volume using a constant ratio of 0·855 for preterm infant is 4%.

As plasma volume measurements may be associated with an error of 6%,[6] a double label technique using a red cell and a plasma indicator probably does not appreciably increase the reliability of whole blood volume estimation. On the other hand, we agree with Dr Anthony and Professor Levene that the use of a plasma protein label would have been more reliable for plasma volume measurement. However, determination of plasma volume was not the primary purpose of our study. Moreover, Evans blue is no longer commercially available and radioactively labelled proteins are not used any more in newborn infants for ethical reasons.

We conclude that the fetal haemoglobin dilution technique is a reliable method for red cell mass measurement and whole blood volume estimation. As blood volume did not change during transfusion, the increase in red cell mass was certainly associated with a decrease in plasma volume. A simple measurement of a change in packed cell volume would not have been as informative as the estimation of blood volume from red cell mass and packed cell volume.

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Non-invasive assessment of pulmonary arterial pressure in healthy neonates

Sir,—We read with interest the study by Skinner *et al*.[1] We would however, take issue with the statement that the method we used in our study to assess pulmonary artery pressure,[2] the inverse relationship with the ratio of the time to peak velocity (TPV) of pulmonary artery flow and the right ventricular ejection time (RVET), is less suitable for study of the newborn. The advantage of TPV:RVET ratio as a means of studying physiological changes is that we obtained quantitative data in 100% of our studies. Using tricuspid regurgitation, Dr Skinner *et al* obtained quantitative data in only 22% of term studies and 45% of preterm studies.

Our data suggested that pulmonary artery pressure falls slightly but significantly more slowly in healthy preterm than in term infants.[2] Dr Skinner *et al* did not find this difference and suggested that factors other than pulmonary artery pressure which can affect TPV:RVET might have influenced our results. We do not believe that to be the case for the following reasons, taking each of these factors in turn. Firstly, that the positioning of the pulsed Doppler sample is critical. We used a constant site in the centre of the artery distal to the pulmonary valve, not technically difficult in early life. Secondly, myocardial function, which if poor will prolong TPV. All infants in the study referred to were healthy and had good myocardial function. Any reduction in contractility resulting from lower gestational age would cause the difference which we found between preterm and term infants to be an underestimate. Thirdly, tricuspid regurgitation, here Dr Skinner *et al* have misread the reference cited. Kitabatake *et al* could find no statistically significant effect of tricuspid regurgitation on the relationship between TPV and pulmonary artery pressure.[3] Finally, heart rate, which will slightly reduce TPV:RVET as it increases.[4] The term babies in our study had a mean heart rate of 129 compared with 143 in those preterm. From the regression analysis provided by the data of Akiba *et al*,[4] this difference would cause a change in TPV:RVET of 0·005, not likely to affect the significance of our data. For example, between 25 and 36 hours after birth mean TPV:RVET was 0·36 in the term infants compared with 0·29 in the preterms. In addition the difference in heart rate between the two groups remained constant through the study period while the differences in TPV: RVET did not.

Tricuspid regurgitation is a good method for estimating pulmonary artery pressure, so why did Skinner *et al* not find the same differences? While lack of longitudinal data may be part of the problem, the important information missing from this paper is the distribution of gestation within the wide range quoted (28 to 35 weeks) and even more importantly the gestation of the seven infants in whom longitudinal quantitative analysis was possible. Healthy infants of less than 31 weeks are not common, this tends to bias the selection of infants in this type of study towards higher gestations. Thirty seven percent of the preterm infants in our study were of less than 31 weeks, this may be why we were able to demonstrate a difference.

Tricuspid regurgitation, when present, and TPV:RVET are both good methods for non-invasively assessing pulmonary artery pressure. Like all Doppler methods they both have limitations. Within the practice of paediatric cardiology, where both methods were developed and validated, tricuspid regurgitation has advantages particularly in children with large intracardiac left to right shunts. However, we would argue that a method which allows data collection in only a minority of normal subjects may not be the best for describing physiological changes.

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1 Skinner JR, Boys RJ, Hunter S, Hey EN. Non-invasive assessment of pulmonary arterial pressure in healthy neonates. *Arch Dis Child* 1990;66:386–90.

2 Evans NJ, Archer LNJ. Postnatal circulatory adaptation in healthy term and preterm neonates. *Arch Dis Child* 1990;65:24–6.

3 Kitabatake A, Inoue M, Asao M, *et al*. Non invasive evaluation of pulmonary hypertension by a pulsed Doppler technique. *Circulation* 1983;68:302–9.

4 Akiba T, Yoshikawa M, Otaki S, *et al*. Prediction of peak pulmonary artery pressure by continuous wave Doppler echo cardiography in infants and children. *Pediatr Cardiol* 1988;9: 225–9.

Dr Skinner et al comment:

We thank Drs Evans and Archer for their comments. There are now three Doppler techniques for assessing neonatal pulmonary arterial pressure: the TPV:RVET ratio, regurgitant tricuspid flow, and the analysis of ductal flow.[1] The TPV:RVET ratio can be measured serially in all infants, but is it as accurate a measure as that provided by tricuspid regurgitation when present and measurable?

If the TPV:RVET ratio is influenced by pulmonary arterial pressure only and it is valid to compare subjects of different size, absolute values can be obtained by imposing Evans' ratios on Kitabatake's regression from adults, which correlates TPV:RVET with pulmonary arterial pressure. However, Evans' ratio of 0·2:1 in preterm infants at six hours implies a mean arterial pressure of 100 mmHg; almost three times average systemic pressure! Similarly, the lower ratios seen in the preterm babies imply higher pressures than in term babies.

As aortic TPV is shortened by mitral regurgitation,[2] Kitabatake postulated that pulmonary TPV might be shortened by tricuspid regurgitation, and found nine of 11 adult patients with tricuspid regurgitation had TPV values below the regression line for the whole group. Although the regression for patients with tricuspid regurgitation did not differ significantly from this regression, a third of the whole group had tricuspid regurgitation. No comparison was reported between those with and without tricuspid regurgitation.

Serial measurement is clearly the best way to assess the speed with which pulmonary arterial pressure falls, and we presented our serial data on seven preterm babies graphically. They were the same mean gestational age

(31·6 weeks) as those studied by Evans and Archer (one at 28, one at 30, two at 32, and three at 33 weeks). Furthermore our results were substantiated by analysis of ductal flow. Unfortunately Drs Evans and Archer did not utilise the potential of their technique for serial measurement to the full; results were presented in a cross sectional manner, with different numbers studied at each age. Group means were compared when it would have been better to analyse the rate of fall in each individual separately.

In truth, neither of these papers can probably come to a definite conclusion about the relative rate of fall of pulmonary arterial pressure in term and preterm babies. However, three potentially useful Doppler techniques have been introduced to neonatology and this discussion helps to clarify some of the potential merits and shortcomings of each.

1 Musewe NN, Poppe D, Smallhorn JF, *et al.* Doppler echocardiographic measurement of pulmonary artery pressure from ductal Doppler velocities in the newborn. *J Am Coll Cardiol* 1990;**15**:446–56.
2 Elkins RC, Morrow AG, Vasko JS, Braunwald E. The effects of mitral regurgitation on the pattern of instantaneous aortic blood flow: clinical and experimental observations. *Circulation* 1967;**36**:45–53.

Accuracy of height measurements

SIR,—In their study of the accuracy of measurements made by health visitors, Ahmed *et al* assume that a reading by a trained auxologist on a Harpenden stadiometer was obtained without error.[1] Not only is this assumption dangerous and unjustified, it is also unnecessary, as the authors' analysis happens to contain an estimate of the error's variability. The column headed 'children' in table 2 of their paper does not, as may be thought, provide the variance of the heights of the children who took part in the experiment. For children selected at random from the population, or even from a day nursery, as in the study, this should be of the order 15–20 cm^2. Moreover, the effect due to a child is removed, in the analysis, by the differencing that occurs when the auxologist's measurement is subtracted from that of a health visitor. The column headed 'children' gives, in fact, the variance of the auxologist's measurement error. Averaging over the rows of the table leads to an estimated standard deviation of 0·31 cm, which is comparable with the values obtained by experienced auxologists in our own experiments.[2]

Not only is this variability not negligible, it is of a similar order of magnitude to that which obtains on instruments such as the Microtoise. The reason, as we have pointed out, is that almost all the variance in a height measurement is due to the elasticity of the child, and very little to the inadequacies of the instrument or the observer. It therefore becomes necessary to talk of estimating not the true height of a child, as the authors do, but the mean height.

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1 Ahmed ML, Yudin PL, Macfarlane JA, McPherson K, Dunger DB. Are measurements of height made by health visitors sufficiently accurate for routine screening of growth? *Arch Dis Child* 1990;**65**:1345–8.
2 Voss LD, Bailey BJR, Cumming K, Wilkin TJ, Betts PR. The reliability of height measurement (the Wessex Growth Study). *Arch Dis Child* 1990;**65**:1340–4.

Mrs Yudkin and Dr Dunger comment:

Mr Bailey and Ms Voss do not appear to be challenging the results of our study but rather questioning whether the label 'children' in table 2 is appropriate. Their suggestion that the variance in the column headed 'children' in this table should be of the order of 15–20 cm^2 is, we believe, misleading. A variance of this size would relate to the actual heights of children, whereas we were concerned only with the variance in child 'biases'; that is, differences between measurements recorded by health visitor and auxologist.

Mr Bailey and Ms Voss have raised an interesting theoretical question, but our study design does not allow its resolution. The main point at issue is whether measurements made by a trained auxologist using the Harpenden stadiometer and applying traction are affected by the child's 'elasticity' as much as measurements made by a health visitor, using a Microtoise or wallchart. Mr Bailey and Ms Voss suggest that they are, by their statement that 'the effect due to a child is removed, in the analysis, by the differencing that occurs when the auxologist's measurement is subtracted from that of a health visitor'. Our standpoint, on the other hand, is that the auxologist's measurement is the best available, and the purpuse of our study was to examine how health visitor measurements compared with this best.

Prolonged low dose indomethacin for persistent ductus arteriosus

SIR,—We reviewed with great interest the article by Rennie and Cooke.[1] The treatment of patent ductus arteriosus remains an important issue in the care of the premature infant. However, we would like to address several areas in order to clarify the results achieved by the investigators. Certain specific descriptions were missing in the methods section that would be helpful in justifying prolonged low dose indomethacin as an alternative treatment.

Our first concern is the basis for the diagnosis of the patent ductus arteriosus and its relapse. While clinical symptoms are important diagnostic parameters, they are subject to observer bias especially in a study spanning different institutions. Echocardiography, the preferred diagnostic method, would strengthen the initial diagnosis and the presence or absence of relapse.[2] This improvement could have provided an important prospective diagnostic definition to describe the patient population more accurately.

Secondly, the many clinical factors that influence the patency of the ductus were excluded.[3] There was no mention of important confounding variables such as fluid management, methods of ventilation, use of exogenous surfactant, or severity of the respira-disease. In addition, the lack of serum indomethacin concentrations leaves an important void in the clinical results.[4]

The premise for this study, to find a safer treatment for the persistent ductus, is applauded. However, the lack of more detailed description of the patients and methods prevents this investigation from the universal acceptance desired by its authors. We would like to obtain the missing information or, if unavailable, suggest that repetition of the investigation controlling for the confounding variables. The results of such a study would provide an alternative way for the management of an all too common neonatal concern.

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1 Rennie JM, Cooke RWI. Prolonged low dose indomethacin for persistent ductus arteriosus. *Arch Dis Child* 1991;**66**:55–8.
2 Bayle BG, Meyer RA, Kaplan S, *et al.* The critically ill premature infant with patent ductus arteriosus and pulmonary disease—an echocardiographic assessment. *J Pediatr* 1975; **86**:423–32.
3 Bell EF, Warburton D, Sonstreet BS, Oh W. Effect of fluid administration on the development of symptomatic patent ductus arteriosus and congestive heart failure in premature infants. *N Engl J Med* 1980;**302**:598–604.
4 Brash AR, Hickey DE, Graham TP, Stahlman MT, Oates JA, Cotton RB. Pharmokinetics of indomethacin in the neonate: the relationship of indomethacin plasma levels to response of the ductus arteriosus. *N Engl J Med* 1981;**305**: 67–72.

Drs Rennie and Cooke comment:

We thank Dr Marino and his colleagues for their interest in our paper. We accept that echocardiographic diagnosis of patent ductus arteriosus would have provided more objective evidence on which to enrol and subsequently assess subjects, but at the time this study was started the technique was not available to us in either centre. We would obviously use this method in any future studies.

The problem of differences in management should have been taken care of by the fact that this study was randomised. Fluid management was fairly uniform, with fluid restriction to 120 ml/kg/24 hours in both centres being used for significant patent ductus arteriosus. During much of the time that this study was in progress we were also recruiting infants to a randomised surfactant trial. The problem of the severity of disease was partly addressed by the demonstration that by chance the long course group tended to be nursed in higher ambient oxygen at enrollment.

We would not agree that serum indomethacin concentrations are essential for the management of patent ductus arteriosus. Our experience with measuring concentrations of this drug[1] confirmed the large and unpredictable variation noted by Brash *et al.*[2] We were unable to establish a threshold at which clinical response was certain and felt that this was due to the fact that even low levels of indomethacin were associated with cessation of prostaglandin synthesis. These observations led to the present study as we felt, like Seyberth *et al* that resurgence of prostaglandin synthesis could be important in relapse.[3]

1 Rennie JM, Doyle J, Cooke RWI. Early administration of indomethacin to preterm infants. *Arch Dis Child* 1986;**61**:233–8.

2 Brash AR, Hickey DE, Graham TP, Stahlman MT, Oates JA, Cotton RB. Pharmokinetics of indomethacin in the neonate: relationship of indomethacin plasma levels to response of the ductus arteriosus. *N Engl J Med* 1981;**305**: 67–72.

3 Seyberth HW, Muller H, Willie L, Pluckthun H, Wolf D, Ulmer HE. Recovery of prostaglandin production associated with reopening of the ductus arteriosus after indomethacin treatment in preterm infants with respiratory distress syndrome. *Pediatric Pharmacology* 1982;**2**: 127–41.

The incidence of renal calcification in preterm infants

SIR,—In the report by Short and Cooke, the 21 infants who developed renal calcification all had bronchopulmonary dysplasia.[1] While Short and Cooke recorded details of steroid usage the relationship between steroid use and renal calcification was not explored. Their failure to do so is indeed surprising as nephrocalcinosis may be one of the side effects of the now widespread use of steroids for bronchopulmonary dysplasia.[2]

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1 Short A, Cooke RWI. The incidence of renal calcification in preterm infants. *Arch Dis Child* 1991;**66**:412–7.

2 Kamitsuka MD, Peloquin D. Renal calcification after dexamethasone in infants with bronchopulmonary dysplasia. *Lancet* 1991;**337**:626.

Drs Short and Cooke comment:
We thank Dr Blumenthal for his interest in our recent article, and note his comments regarding the use of steroid treatment. The hypercalciuric effects of steroids have been utilised for many years in the treatment of hypercalcaemia in adult patients. We certainly considered the possible effects of such treatment in our own patients, and recorded dosage and duration of dexamethasone treatment.

The small number of patients with dexamethasone (two infants with bronchopulmonary dysplasia who developed calcification, and one who did not), however, preclude any useful comment upon the effects of such treatment in our study. In the two patients with renal calcification who received dexamethasone, renal ultrasound scans were normal before treatment, but we would be reluctant to postulate a direct causal relationship between steroid therapy and calcification. We would agree, however, that the increasing use of steroids provides an additional argument for close evaluation of the renal tract in all preterm infants at risk of renal calcification.

Who pioneered the use of alternative donors (and stem cells from peripheral blood) in bone marrow transplantation?

SIR,—Dr Hows writes her opinion that 'The Seattle group has pioneered the use of partially matched family donor transplants . . .' and perhaps that reflects her own experience, mainly in adult transplantation.[1] As far as is known to us, the first successful bone marrow transplant from a father to a son was inspired by Professor J R Hobbs and undertaken on 29 August 1972 by the Westminster Bone Marrow Team for Mark Pegram who had severe combined immune deficiency; the late Dr Iain Anderson was the consultant paediatrician and the late Professor James G Humble was the haematologist. Despite a stormy graft-versus-host disease (GVHD) in which bilirubin concentration rose to 118 µmol/l, Mark has survived to the present day with no evidence of chronic GVHD and has enjoyed a normal healthy life and currently plays rugby. He was probably the first human to be treated after bone marrow transplantation with antilymphocyte globulin.[2] In 1985 the team published a series of 50 patients engrafted from genetic haplotype-sharing donors,[3] and these were mostly for paediatric patients with longer survivals than the 40 in the Seattle paper.[4]

The first intended HLA matched mixed lymphocyte culture negative transplant from a volunteer unrelated donor to produce an engrafted survivor was conceived by Professor J R Hobbs and undertaken on 13 April 1973 for Simon Bostic who had chronic granulomatous disease; Dr Kenneth Hugh-Jones was the consultant paediatrician, Dr David James was responsible for the HLA tissue typing, and (now) Professor Masaichi Yamamura perfected the mixed lymphocyte culture method[5]; the case was not reported in full until 1977.[6] Cyclophosphamide only was used for the induction to avoid total body irradiation which has more unpleasant sequelae for children, and it was thus discovered that this could only displace some 12% of the human host marrow, so that there was only engraftment of some 12% of the healthy female donor's neutrophils. Neutrophil counts, nevertheless, were $0\cdot7$–$1\cdot5\times10^9$/l and were identified by Professor Humble as they not only contained female 'clubs' but could be shown by double staining to be strongly nitroblue tetrazolium positive in contrast to the majority of the totally negative host cells. An almost identical result has since been reported.[7] Such a good neutrophil count kept Simon completely free of life threatening infections and off all antibiotics for some six years, by which time the chimeric state had petered out and the nitroblue tetrazolium positive cells could no longer be detected. During that period, Simon flourished and grew normally and his lymphocytes remained mixed lymphocyte culture negative against his donor when tested on seven occasions. With the final disappearance of the donor cells, Simon relapsed to his former severe illness developing liver and lung abscesses which responded to the introduction of intensive antibiotic treatment and subsequent prophylaxis, but thereafter his growth rate deteriorated and never again reached normal. He has gained adulthood with modern care but when recently tested did not show much evidence of inducibility of increased staphylococcal killing capacity by the use of interferon gamma.[8] His donor, Mrs Joan Macfarlane, went on to add two further children to the one she had at the time she volunteered, and, presumably as a result, she became mixed lymphocyte culture positive against Simon so was not used for a second graft.

A second boy with severe chronic granulomatous disease engrafted for three months after a transplant on 19 February 1975 from another matched volunteer unrelated donor and also derived immense benefit from the procedure to enjoy seven years of childhood before dying of cor pulmonale, and an adult similarly had correction of his severe aplastic anaemia after a transplant in November 1975. A fuller account of the introduction of volunteer unrelated donors appears in *Correction of Certain Genetic Diseases by Transplantation, 1989* a symposium report distributed by the Westminster Medical School Research Trust, 17 Horseferry Road, London SW1P 2AR. It gives the true credit for the initiation of the first volunteer unrelated donor panel to the mother of Simon Bostic, Mrs Elisabeth Bostic, after the near miss when Professor Hobbs had proved a mixed lymphocyte culture negative matched unrelated donor from Holland for her first affected son, Andrew, who died just a few days before the graft could be undertaken in 1972. After Elisabeth's death, full credit should then be maintained for the stoic work of Mrs Shirley Nolan who took up the fund raising to enable Dr James to build it up to its world famous size. On the above evidence, surely credit for pioneering the use of alternative donors belongs to Professor John R Hobbs and the Westminster Bone Marrow Team, who still enjoy the world's best survivals from children so treated.

Incidentally, Hobbs was also responsible for the first transplant using stem cells of the peripheral blood, taken from a 4 year old donor in June 1970 to treat a boy with type I mucocutaneous candidiasis (migration inhibition factor is completely absent) a disease which has proved fatal in all our other cases who were not transplanted. The treated patient remains alive and well as the longest living survivor of a matched sibling transplant in Britain and Dr Hows might have noted that this transplant was done at the Hammersmith Hospital[9] before she arrived.

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1 Hows JM. Paediatric bone marrow transplantation using donors other than HLA genotypically identical siblings. *Arch Dis Child* 1991;**66**: 546–50.

2 Hobbs JR, Humble JG, Anderson IM, James DCO, Yamamura M. The elective treatment of graft-versus-host disease following a bone marrow graft from a father to a son with severe combined immunodeficiency. *Postgrad Med J* 1976;**52**(suppl 5):90–4.

3 Hobbs JR, Williamson S, Chambers JD, *et al.* Use of donors sharing one genetic haplotype for bone marrow transplantation. *Tokai J Exp Clin Med* 1985;**10**:207–14.

4 Beatty PG, Clift RA, Michelson EM, *et al.* Marrow transplantation from donors other than HLA identical siblings. *N Engl J Med* 1985;**313**:765–71.

5 Yamamura M, Nikbin B, Hobbs JR. Standardisation of the mixed lymphocyte reaction. *J Immunol Methods* 1976;**10**:367–78.

6 Foroozanfar N, Hobbs JR, Hugh-Jones K, *et al.* Bone marrow transplant from an unrelated donor of chronic granulomatous disease. *Lancet* 1977;**i**:210–3.

7 Kamani N, August CS, Campbell DE, Hassan NF, Douglas SD. Marrow transplantation in chronic granulomatous disease: an update with six year follow-up. *J Pediatr* 1988;**113**:697.

8 Ezekowitz RAB, Dinauer MC, Jaffe HS, *et al.* Partial correction of the phagocyte defect in patients with X-linked chronic granulomatous disease by subcutaneous interferon gamma. *N Engl J Med* 1988;**319**:146–51.

9 Valdimarsson H, Moss PD, Holt PJL, Hobbs JR. Treatment of chronic mucocutaneous candidiasis with leucocytes from HL-A compatible sibling. *Lancet* 1972;**i**:469–72.

Dr Hows comments:
I am grateful to Drs Hughes-Jones, Selwyn, and Riches for their account of the pioneering role of Professor Jack Hobbs and other members of the Westminster Bone Marrow Transplant Team in the use of alternative marrow donors in paediatric bone marrow transplantation.

I tried to write a short 'state of the art' annotation of this specialised area which might be of practical use to paediatricians with a general interest in haematology. The emphasis is therefore on current concepts of donor selection and recent results.

Regrettably in this type of communication there is no space to address interesting historical perspective such as that provided by the Westminster team. Their experience would certainly take pride of place in a full length review article.

District handicap teams: impediments to progress

Sir,—Of the reasons discussed by Bax and Whitmore for lack of progress in setting up Court type district handicap teams,[1] much the most important is the inability or unwillingness of many doctors to contribute to effective interdisciplinary work. Education and social service departments are reluctant to commit resources to child development centres, especially those on hospital sites, because they anticipate medical domination of operational policy (referrals, etc), day to day management, and 'patient care' decision making. It would take much more than a 'commitment to provide a peripatetic service in satellite premises' to offset these reservations.

Similarly, professionals employed by education and social services are disinclined to recognise a divine right of doctors to be in charge under all circumstances, and are unlikely to work with enthusiasm in such an environment. A senior social worker, himself committed to interdisciplinary working, said to me recently, 'a doctor's definition of a team is a group of people working together whom he/she (the doctor) tells what to do'. The joke is on us, but it is really not at all funny.

Bax and Whitmore think that the Court committee's concept of a *district handicap team* was sound: I agree (I was a member of the committee) in the historical context of the late 1970s. Much has happened since then, however, and the changes in thinking and practice reflected in the Education Act 1981, the Disabled Persons' Act 1986, and the Children Act 1989 require that responsibilities for the management of childhood disability are shared far beyond the health services terms of reference of the Court committee. Of course the medical and health related contribution continues to be crucial and even pivotal in many instances, especially in early childhood. Unless we collectively are more whole hearted and less professionally arrogant in our attitude to interdisciplinary work, however, our influence will increasingly be marginalised. We risk being consulted rather than involved, which would jeopardise comprehensive care: the ultimate losers would be the children and their families.

The *child development centre* is a medical model (for example, in siting and referral procedures), and therefore inappropriate on its own for the 1990s. Bax and Whitmore also acknowledge some of the problems of trying to cater for children of all ages in a single centre. How indeed do you combine suitable decor, furniture, equipment, and comprehensive service provision for infants and toddlers, preschool and school children, and adolescents all under one affordable roof?

I suggest that the way ahead is to develop a suitably updated concept of *teams* which work flexibly in different contexts and premises, one of which might well be a 'centre' on a hospital site where facilities for early medical identification and diagnosis are linked with the initial stages of treatment and ongoing assessment.

Interagency discussions about the Children Act, present us *now* with excellent new opportunities to create or reinforce effective teamwork. Doctors involved in this collaboration need to be sure that they do not take any pedestals with them.

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1 Bax MCO, Whitmore K. District handicap teams in England: 1983–8. *Arch Dis Child* 1991;**66:** 656–64.

District handicap teams in England 1983–8

Sir,—We wish to make it clear that in our article on district handicap teams[1] our third recommendation (p664) is that the child development centre should initially be able to cater for the needs of all children under 16 years (not under 10 as stated) and for older children in the absence of adequate similar facilities for disabled adolescents.

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1 Bax MCO, Whitmore K. District handicap teams in England: 1983–8. *Arch Dis Child* 1991;**66:** 656–64.

Major problems with paediatric bed usage statistics?

Sir,—MacFaul and Long show that paediatric bed occupancy in two children's wards in Pinderfields Hospital can be calculated in five different ways, giving results ranging from 73% to 106%, depending on the treatment of empty beds and bed borrowing between specialties.[1]

Interesting as the exercise is, Dr MacFaul and Mr Long might ask their district management why such calculations should be necessary. The Körner committee recommended in 1982 that empty beds should no longer be allocated to a specialty.[2] Allocation of beds to specialties should be seen as a statement of operational planning intent and does not have to correspond to beds physically occupied or unoccupied, counted on a daily basis.[3]

Because of flexible use of beds between specialties, it is necessary to distinguish between *ward* bed occupancy and *specialty* bed occupancy. Ward occupancy is calculated as:

$$\frac{\text{occupied bed days in ward}}{\text{available bed days in ward}}$$

for each ward. This gives, as McFaul and Long show, 54% for ward A and 69% for ward B in their example. Specialty occupancy is calculated as:

$$\frac{\text{occupied bed days in any ward}}{\text{allocated bed days for specialty}}$$

In the Pinderfields example, on the information given, this is:

$$\frac{\text{949 (ward A) + 3074 (ward B) + 201 (intensive care and other)}}{\text{5187 (allocated to paediatrics)}}$$

giving a paediatric bed occupancy over the period shown of 81%. This method follows not only 'the spirit of Körner', but also the letter.

This level of occupancy is well above the optimum of 75% for acute children's services mentioned in Health Building Note 23[4] and supports concerns about a possible shortage of capacity to deal with peaks in demand.

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1 MacFaul R, Long R. Major problems with paediatric bed usage statistics? *Arch Dis Child* 1991;**66:**504–7.
2 Steering Group on Health Services Information (Körner Committee). *First Report to the Secretary of State: a report on the collection and use of information about hospital clinical activity in the NHS.* London: HMSO, 1982:141.
3 Health Services Information Branch. *User's guide to statistics about the clinical activity of departments and services provided on or off a hospital site.* London: Department of Health, 1988:173.
4 Department of Health and Social Security. *Health building note 23: hospital accommodation for children.* London: DHSS, 1984.

Dr MacFaul and Mr Long comment:
We thank Mr Glickman for his helpful comments on our paper. It is indeed the case that the Körner committee recommended that it should no longer be required that unoccupied beds be attributed to a specialty. Furthermore, it was recommended that bed occupancy statistics cease to be used as a measure of efficient bed usage (Körner first report para 9.39.)[1] However, in Yorkshire Regional Health Authority, bed occupancy measures were reintroduced in response to demand from health authorities: hence the development of the modified SH3 (YSH3B) referred to in our paper. It is a concept with which clinicians are familiar and bed occupancy possibly identifies more readily shortfall of specialty paediatric bed allocation over peak bed usage periods. Hence it was used in this paper. One main point of the paper, however, was to identify the variation in interpretation of Körner recommendations which may occur within a district—thereby limiting the value of *between*—district indicators. Mr Glickman's calculation of occupancy disregards, as Körner advised, any allocation of empty beds to a specialty but he does necessarily include the nominal allocation of beds for use by the specialty. Such allocation is also necessary to calculate throughput (throughput is calculated in terms of number of beds that the specialty was intended to use, rather than the beds estimated to be available). For patients with the same length of stay during the study period report in our paper, throughput figures varied considerably (between 23·83 and 34·68) according to the way in which the notional allocation of beds was made between two wards. The throughput figures based on the calculations used by Mr Glickman are given in option (1) in our paper.

Using the maximum flexibility—our option (5)—the highest throughput and bed occupancy figures were achieved. This maximum flexibility of usage seems more clearly to be in the spirit of Körner. A further and most important point evident from the study was the significance of when, in the 24 hour period, a count of patients was made and how complete such a count proved to be.

Since the recommendation made in the Health Building Note 23 in 1984, there has been steadily decreasing duration of stay in paediatric medicine. It is not clear what an optimal bed occupancy or throughput should be in order to be able to achieve adequate capacity to accommodate children in children wards over peak periods of usage.

1 Körner E, chairman. NHS/DHSS steering group on health services information. *First report.* London: DHSS, 1982.

Neonatal diaphragmatic paralysis caused by chest drains

Sɪʀ,—Arya *et al* attributed bilateral phrenic nerve palsy to the insertion of chest drains.[1] Although they elegantly proved dysfunction in both phrenic nerves, they provided no evidence of a causative association with the insertion of the chest drains.

Both phrenic nerves are closely related to major vessels and the pericardium within the mediastinum[2] and therefore damage affecting the phrenic nerves alone would seem unlikely.

An alternative explanation would be stretching of the phrenic nerve caused by a tension pneumothorax increasing the distance from the nerves' origin to its insertion.

Finally it would not seem very likely for a process which is very uncommon, only having been described on two previous occasions, to occur twice in the same patient.

Surely it is dangerous to attribute events to an iatrogenic cause, with the possible implications of this, when an alternative explanation involving the natural history of the underlying disease is possible.

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1 Arya H, Williams J, Ponsford SN, Bissenden JG. Neonatal diaphragmatic paralysis caused by chest drains. *Arch Dis Child* 1991;**66**:441–2.
2 Williams PL, Warwick R, eds. *Gray's anatomy.* London: Churchill Livingstone, 1980.

Dr Bissenden comments:

I would accept that our case report did not prove that chest drains caused the phrenic nerve damage. It merely demonstrated bilateral phrenic nerve paralysis in a baby who had chest drains which reached the mediastinum. We suggested the chest drains caused the problems in the absence of another explanation. The alternative suggestion that a tension pneumothorax caused the phrenic nerve damage of such duration is more unlikely than our explanation, so until someone comes up with something better, ours is the best I have heard so far.

Children choking on foreign bodies from toys

Sɪʀ,—There is interest in the problem of aspiration of foreign bodies from toys. Manufacturers and trading standards officers raise practical issues about the size of items that might cause choking, the risks of hair or pile fabrics on toys, and the attractiveness to children of items which might imitate food. It is not known how common these incidents are. This is relevant to the European Toy Safety Standard EN71, which is currently under review. Unfortunately the Department of Trade and Industry's Home Accident Surveillance System (HASS), which analyses a sample of cases attending accident and emergency departments does not provide satisfactory information. This is because choking is combined with ingestion and insertion of foreign bodies into body orifices under a general heading 'foreign bodies'.

We therefore undertook a study of incidents of choking in childhood for the year 1989 in Wales to estimate whether aspiration of foreign bodies from toys and toy parts was common. Letters were sent to all 60 consultant paediatricians and ear, nose, and throat surgeons in Wales asking them for details of children who were admitted to hospital after choking on foreign bodies. Replies were obtained from 50 consultants (83%). Only four recalled any cases of choking, none of which was related to toys.

We also inquired whether the consultants had ever seen such an incident related to toys. Only one doctor recalled such an incident and this was due to a small bead. There were no instances of choking due to hair from a toy.

We conclude that incidents of choking due to parts or hair from toys must be rare and are not a major problem in the UK.

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Accidental poisoning in children

Sɪʀ,—Drs Sibert and Routledge are correct.[1] Childhood poisoning should be classified and managed according to the estimated intake and severity rating of the ingested toxin. Poisoning events might be classified as follows:

(1) Poisoning scare. Tablets or medicine spilt. No ingestion. Poisoning non-event. Frequent.
(2) Minimal ingestion. Few ml or few tablets. No symptoms or signs. Common.
(3) Moderate ingestion. No apparent sequelae. Common.
(4) Severe ingestion. Toxic agent in significant amount. Infrequent.

We have found that use of observation beds in the casualty department is adequate for groups 1, 2, and 3 and resulted in a 74% reduction in admission rates between 1975 and 1980.[2] Our recent study of 206 ingestions showed that 75% of children suspected of ingesting drugs were given syrup of ipecacuanha, 3% had gastric lavage, and 18% received no treatment.[3] Seventy one per cent of children were observed and discharged. Of the remainder, 25% were admitted to a medical ward and 4% to intensive care. Poison reference centres are usually staffed and briefed by adult orientated people. Their management advice is frequently excessive and interventional, based on adult experience of severe intentional overdose as compared with childhood accidental and usually trivial ingestion.

The bottom line in poisoning is to take care, to treat children and chemicals with cautious respect, and, if in doubt, to admit and observe. Delayed release psychotherapeutic agents should be treated with particular caution.

Finally, should laburnum be classified as 'potentially very toxic'?

H RFIDAH
D GILL
Department of Paediatrics,
Royal College of Surgeons in Ireland,
123 St Stephen's Green,
Dublin 2

1 Sibert JR, Routledge PA. Accidental poisoning in children: can we admit fewer children with safety? *Arch Dis Child* 1991;**66**:263–6.
2 Gill D. Changing pattern of poisoning in children. *BMJ* 1983;**287**:1468.
3 Rfidah H, Casey P. Tracey JA, Gill D. Childhood poisoning in Dublin. *Irish Med J* 1991 (in press).

Hyperexplexia or stiff baby syndrome

Sɪʀ,—I am sure that other people will write to you to tell you that the spelling of the condition referred to recently in the journal is incorrect.[1] It should be 'hyperekplexia', 'ekplexia' is the Greek for startle, whereas 'explexia' does not mean anything at all! The present article perpetuates mis-spelling that has appeared in several other contributions on this subject.

S J WALLACE
Department of Child Health,
University Hospital of Wales,
Heath Park, Cardiff CF4 4XW

1 Tohier C, Roze JC, David A, Veccierini MF, Renaud P, Mouzard A. Hyperexplexia or stiff baby syndrome. *Arch Dis Child* 1991;**66**:460–1.

The technical editor comments:

The dictionary we use for the journal is *Dorland's Illustrated Medical Dictionary*, which is American; this gives the spelling as hyperexplexia. We do 'adjust' the spelling of words like apnea and anemia to conform with 'English' spelling but otherwise we try to follow Dorland's 'style'.

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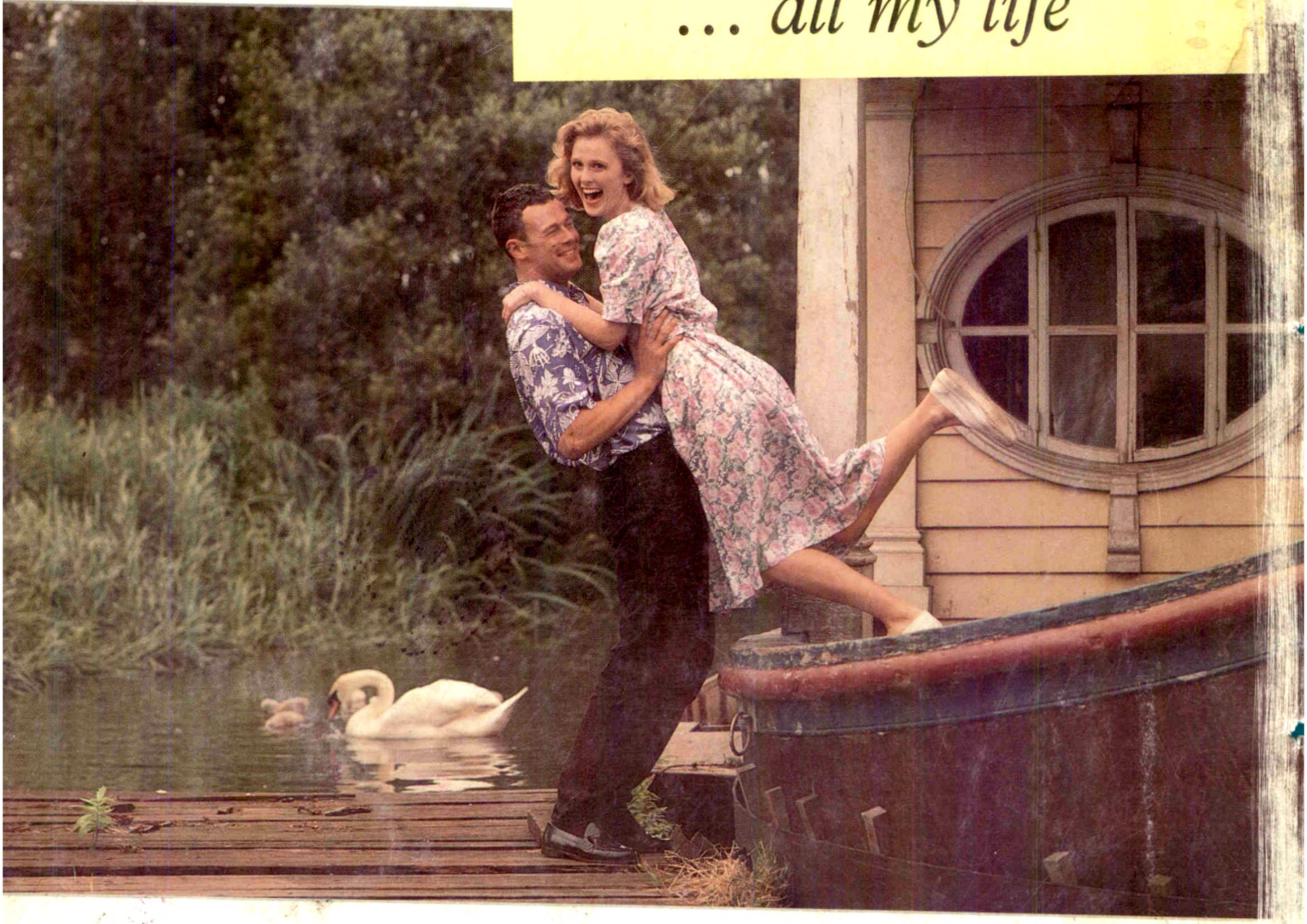

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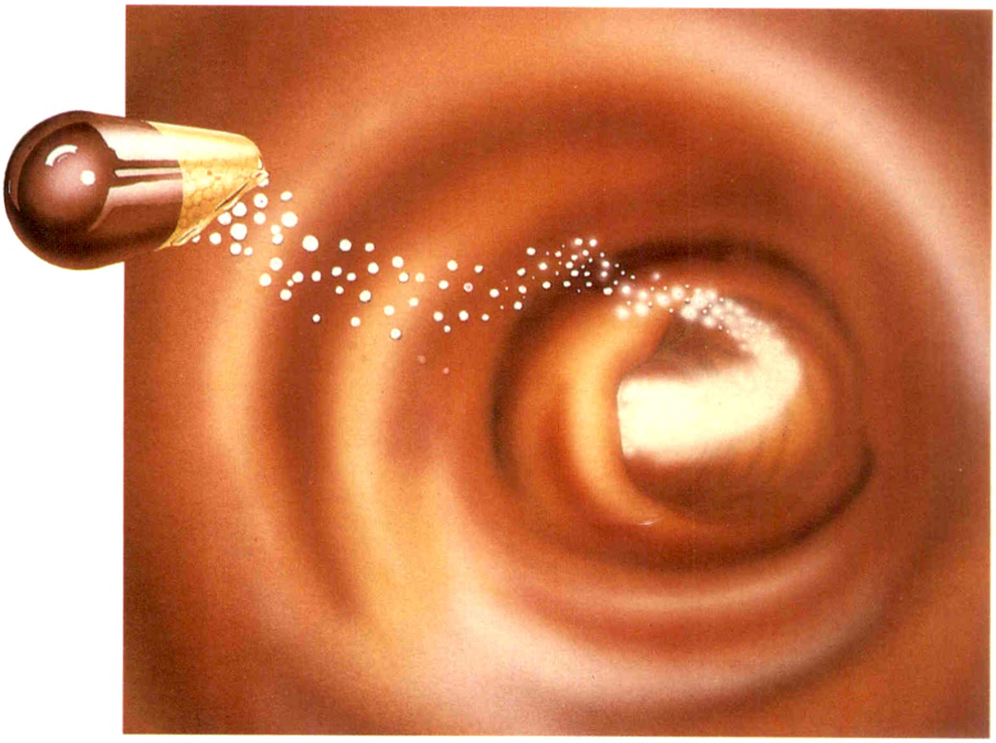

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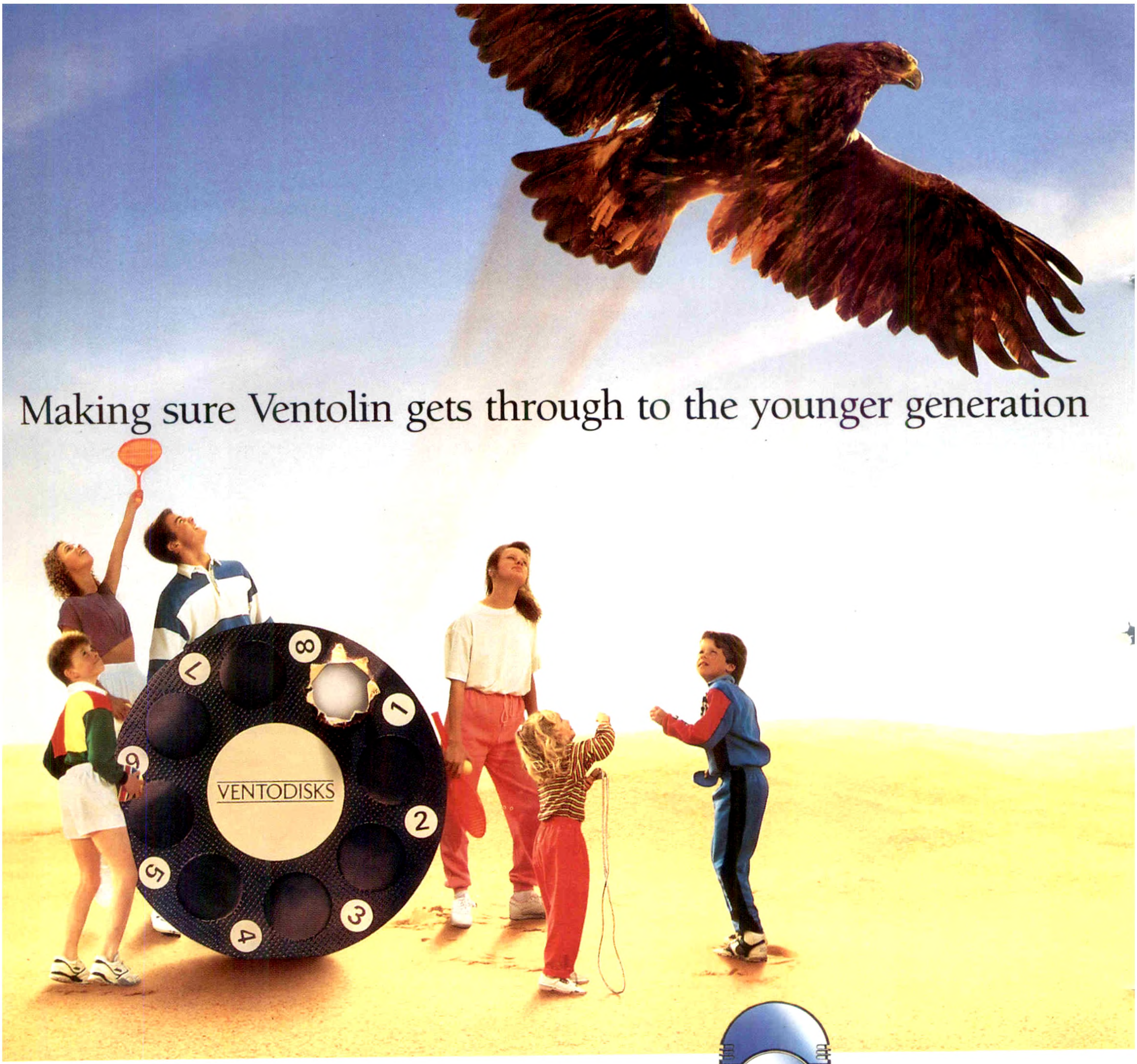
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Annotations

Kawasaki disease: recent advances

It is now 20 years since Dr Tomisaku Kawasaki first reported a series of Japanese children with an illness he called 'acute febrile mucocutaneous lymph node syndrome',[1] but which is now more commonly referred to as Kawasaki disease.[2] The disorder has since been recognised to be an important and relatively common childhood illness, occurring worldwide, and with a greatly increased prevalence in Japan.[3 4] The association of Kawasaki disease with coronary artery aneurysms, coronary thrombosis, and myocardial infarction[5] has made the disorder an unusually worrying one and has led to considerable efforts to establish its cause.

In the past few years there have been exciting advances in the understanding of the epidemiology, pathogenesis, clinical spectrum, and treatment of Kawasaki disease. The purpose of this article is to review briefly some of these important advances, which are of relevance to paediatricians in this country.

Epidemiology

Detailed epidemiological studies on Kawasaki disease have been undertaken in many countries. In Japan, where over 80 000 cases of the disease have been reported, the large number of cases and widespread public awareness of the disorder have made possible very accurate documentation of its epidemiology.[4] The disease occurs in epidemics every three years, with peaks in 1979, 1982, and the winter of 1985/86. During these epidemics cases were reported in Japan at a rate of 750 per month and in the interepidemic periods 150–200 cases were reported each month. The epidemics spread in wave like fashion with peaks occurring sequentially in different regions of the country over a period of months. Children aged 6 months to 5 years of age were predominantly effected, with the peak incidence being in children 9 to 11 months of age. Similar epidemicity and clustering of cases has been observed in studies in the USA, Canada, and Europe.[6 7] Despite the obvious epidemic nature of the disease, person to person transmission has not been observed, and secondary cases occurring in contacts of affected patients are extremely rare. Kawasaki disease occurs in siblings of affected patients more frequently than in the general population (2% *v* 0·19% in Japan), with the highest incidence being in siblings under 2 years of age in whom 8–9% develop the illness.[8] Over 50% of affected siblings develop the illness within a few days of each other suggesting common exposure rather than secondary transmission. The occurrence of epidemics, the specific age group affected, and wave like spread of the epidemic strongly suggests that Kawasaki disease is caused by an infectious agent. However, in view of the lack of secondary cases, the agent responsible must be either one of low communicability, or one which only causes the complete clinical picture of Kawasaki disease in a small proportion of affected patients.

Family studies

The possibility that Kawasaki disease represents an unusual reaction to common infectious insults has been investigated by attempting to define a genetic basis for the disorder. Early reports of an association of Kawasaki disease with HLA-BW22 or BW54 have not been confirmed in subsequent studies.[9 10] Persuasive evidence against a genetic basis came from twin studies, in which monozygotic twins in Japan showed no increased concordance for the disorder over dizygotic twins.[11] Although a genetic basis for the disorder seems unlikely, American children of Japanese descent have a significantly increased risk of the condition[12] as indeed do children of Japanese families in the UK.[13] This together with the high incidence in Japan may indicate a racial predisposition.[12 13]

Aetiology

The clinical features of an acute self limited febrile illness with rash, mucous membrane involvement, lymphadenopathy, and leucocytosis, together with the epidemiological features, suggest an infectious aetiology. However, the failure to identify a causative organism using conventional culture and serological techniques, and the lack of response to antibiotics indicates that the disorder is probably not due to any known bacterial or viral pathogen. Early reports documented rickettsia-like bodies on electron microscopy of lymph nodes from patients with Kawasaki disease,[14] but these observations were not confirmed by others. Similarly an association between house dust mite exposure and Kawasaki disease has not held up to closer scrutiny. Epidemiological evidence linking Kawasaki disease to recent carpet shampooing, an activity that may aerosolise mites or mite associated organisms, was also not substantiated in more recent studies.[6 15 16]

In 1983, Kato *et al* reported isolation of a variant strain of *Propionibacterium acnes* from blood cultures taken early in the illness.[17] *P acnes* is a normal skin commensal which does not usually require any special techniques for its isolation.

The failure of other workers to isolate this organism from children with Kawasaki disease led to some scepticism about its possible role in the disorder. However, Kato and his colleagues have more recently reported that the strains of *P acnes* isolated from patients with Kawasaki disease produce an unusual cytotoxin not commonly produced by strains isolated from other sources.[18] The possibility that Kawasaki disease is caused by a toxin elaborated by what are normally commensals or commonly harboured pathogens of low virulence is not without precedence. Staphylococcal toxic shock syndrome, scarlet fever, and the scalded skin syndrome are examples of toxin induced disease which have obvious clinical similarities to Kawasaki disease. The toxins that cause the staphylococcal and streptococcal toxic shock syndromes are now known to belong to a family of enterotoxins which are produced by a variety of different strains of bacteria. These toxins have a common mode of action, binding to specific V-beta regions of the T cell receptor in conjunction with major histocompatibility complex class 2 antigens and acting as superantigens to induce T cell proliferation and cytokine release.[19] As will be discussed below, the immunological findings in Kawasaki disease are similar to those which are induced by the family of enterotoxins, and this, together with the clinical similarities to known enterotoxin disease, raises the possibility that a similar toxin may cause Kawasaki disease.[19]

The association of Kawasaki disease with abnormalities of cellular immunology led to speculation that the disorder might have a retroviral aetiology. In close succession Shulman and Rowley in Chicago,[20] and Burns *et al* in Boston,[21] reported detection of reverse transcriptase activity in culture supernatants of lymphocytes from patients with Kawasaki disease. Reverse transcriptase is the enzyme which synthesises DNA from an RNA template and is the enzyme characteristically produced by retroviruses. These reports raised the exciting possibility that Kawasaki disease may be yet another disorder to emerge from the 'Pandora's box' of retrovirology. With the current interest in AIDS and retrovirology in general this possibility has stimulated an enormous amount of interest. The epidemiological features of Kawasaki disease would be unusual for a retroviral infection because most known retroviral induced illnesses have prolonged incubation periods and cause chronic and persistent illness rather than the acute self limited illness that is seen in Kawasaki disease. Furthermore a number of more recent studies have failed to identify evidence of a retroviral infection,[22] and it now appears likely that the reverse transcriptase activity detected by Shulman and Rowley and Burns is not specific for viral reverse transcriptase but may instead be due to cellular polymerases.

Pathogenesis

Attempts to understand the pathogenesis of Kawasaki disease have focused on the mechanisms causing the major pathological feature, a vasculitis affecting small and medium sized blood vessels, not only in the coronary circulation but in many other organs of the body. The vasculitis, with endothelial cell necrosis, leucocytic infiltration into the media and adventitia of arteries and venules, and medial disruption, often coexists with dilatation of the blood vessel and intraluminal thrombosis.[23] A number of cellular and humoral immunological abnormalities have been documented during the acute phase of Kawasaki disease. These include deficient T8 positive suppressor/cytotoxic T cells, increased T4 positive activated helper T cells bearing HLA-DR surface antigens, and grossly increased numbers of B cells spontaneously secreting IgG and IgM.[24] Immune complexes have been detected in the circulation two to four weeks after onset of the disease in several studies.[25] Our own studies documented that IgG immune complexes detectable in the circulation of patients with Kawasaki disease were able to induce platelet activation and release of vasoactive mediators. Furthermore there appeared to be an association between the presence of immune complexes and the characteristic thrombocytosis occurring in the second and third week of the illness.[26] Raised plasma concentrations of the cytokines interleukin-1 and tumour necrosis factor and spontaneous in vitro production of cytokines by T cells from patients with Kawasaki disease have also been documented.[27 28]

The presence of vasculitis has focused the attention of several workers on the mechanisms of endothelial injury. Leung *et al* demonstrated endothelial cell toxicity of Kawasaki serum for cultured endothelial cells treated with interferon gamma[29] and activation of endothelial cells to express adhesion molecules.[30] In studies conducted at the Institute of Child Health, London, antiendothelial cell antibodies as well as antineutrophil antibodies have also been shown to be present.[31 32] Although the precise pathophysiological sequence involved in the pathogenesis of the vascular damage is far from clear, it seems likely that activation of inflammatory pathways may contribute to the vascular damage and this may offer several sites for therapeutic intervention.

Prognosis

While the aetiology and pathogenesis of Kawasaki disease remain incompletely understood, the clinical spectrum of the disorder and its long term prognosis and treatment are becoming increasingly well defined. Coronary artery aneurysms are demonstrable echocardiographically in 20% to 40% of patients during the acute phase of the disease and 10% to 20% have demonstrable aneurysms during convalescence.[33] Most of the aneurysms appear to regress (at least echocardiographically) during the first year or two after the acute illness. However, a significant number of patients have persistently demonstrable abnormalities for several years. The mortality for coronary artery thrombosis in the acute and early convalescent phase is about 1%. A significant number of patients also have asymptomatic myocardial infarction. Patients with chronic myocardial ischaemia caused by coronary artery stenosis occurring during the healing of a previous aneurysm are increasingly recognised.[34 35]

The long term prognosis for patients with coronary artery abnormalities who recover from the acute illness is not yet known. An important question is whether patients whose coronary arteries have been damaged by Kawasaki disease will have an increased risk of myocardial infarction in later life. A study of children dying of unrelated causes, who were known to have had Kawasaki disease previously, confirmed that histological abnormalities were still present in the coronary arteries several years after the acute illness.[36]

Diagnostic criteria for Kawasaki disease

(A) Fever of five or more days' duration
(B) Presence of four of the following five conditions:
    (1) Bilateral conjunctival injection
    (2) Changes in the mucous membranes and upper respiratory tract, such as injected pharynx, dry cracked lips, strawberry tongue*
    (3) Changes of the peripheral extremities including oedema, erythema, desquamation (may occur later)*
    (4) Polymorphous rash
    (5) Cervical lymphadenopathy
(C) Exclusion of: staphylococcal and streptococcal infection, measles, leptospirosis, and rickettsial disease

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*One of these is sufficient.
Note: in the presence of coronary artery aneurysms detected echocardiographically (A) plus three of the four criteria in (B) is diagnostic.

The abnormalities included thickening and hyperplasia of the intima and media of the artery. Furthermore there are increasing reports of deaths in early adult life due to myocardial infarction in individuals who had Kawasaki disease in infancy.[37] This raises the worrying possibility that coronary arteries damaged during Kawasaki disease may remain abnormal for many years and may predispose to coronary artery disease in early adult life.

One worrying development has been the recognition in recent years that patients with the complete clinical picture may be only the tip of the iceberg, and that other children affected by the same process may present with only some of the diagnostic features.[38] These patients who may have non-specific features such as fever and rash may still develop coronary artery aneurysms or die of the disorder. The recognition of this group of patients, and the diagnosis of their disorder, is obviously even more difficult than the diagnosis of classical Kawasaki disease.

Treatment

Fortunately the otherwise gloomy picture of a disease of unknown aetiology with dire consequences is brightened by the availability of treatment that may considerably reduce the risk of coronary artery disease. Initial studies undertaken in Japan showed that intravenous gammaglobulin infusions given in high dosage in the early phases of the disorder reduced the incidence of coronary artery aneurysms.[39] Subsequent studies both from Japan and the USA have confirmed the beneficial effect of intravenous immunoglobulin, and this is now considered standard treatment for the disorder in many centres.[40 41] Aspirin and perhaps other antiplatelet agents are widely believed to reduce the risk of coronary artery thrombosis, although there have been no controlled trials to confirm their efficacy. In patients who do develop myocardial thrombosis or severe myocardial ischaemia, treatment with antithrombotic agents, thrombolytic drugs and, in some cases, coronary artery surgery have been beneficial.[34 42]

Implications

What are the implications of this information for paediatricians in the UK? Kawasaki disease is almost certainly grossly underdiagnosed in this country. While the incidence in the UK is 1·49 per 100 000 children, it is a lamentable epidemiological fact that a large proportion of cases of Kawasaki disease in the London area, up to 1984, were diagnosed by one paediatrician (the late William C Marshall). Failure to diagnose the disorder or distinguish it from other febrile exanthems of childhood may not have been of great importance while effective treatment was not available. However, in view of the reduction of coronary artery aneurysms by intravenous immunoglobulin and probably a reduction in mortality by aspirin and other antiplatelet agents, it is now of great importance that the disease be recognised early. While cases are most easily diagnosed in the second and third week when desquamation is occurring, this is probably too late to initiate treatment with immunoglobulin, which has been shown to be beneficial when given within the first 10 days of the illness. It is therefore imporant that the diagnosis be considered early. Physicians with experience of Kawasaki disease can usually recognise the disorder on its clinical features in the first 10 days of the illness. Suspected cases should therefore be discussed with, or referred to, a paediatrician with some experience of the disorder as soon as the possibility of the diagnosis is entertained. Investigations to exclude illnesses with similar manifestation, including staphylococcal and streptococcal disease, leptospirosis, and rickettsial disease should be promptly undertaken. Echocardiography to detect coronary artery dilatation or aneurysms should be undertaken as soon as possible, not only in children with the classical features of Kawasaki disease but also in infants with a prolonged febrile illness and two or three of the diagnostic features. Coronary artery abnormalities are easily visualised by experienced paediatric echocardiographers. However, cardiologists without considerable experience in paediatric echocardiography are unlikely to exclude reliably coronary artery disease in small children. As the finding of coronary artery aneurysms have both immediate and long term implications, patients in whom Kawasaki disease is seriously considered should be referred to a centre where the necessary echocardiographic expertise is available. As coronary artery aneurysms can develop as late as six weeks into the illness, patients with an initially normal echocardiographic study should have this repeated six weeks after the onset of the disorder.

There is a general consensus that aspirin should be started as soon as the diagnosis is considered. Recommended doses vary from 30–100 mg/kg/day in the acute stage reducing to an antiplatelet dose of 2 to 5 mg/kg/day once the fever has declined. Many centres prescribed dipyridamole in a dose of 5–10 mg/kg/day as an additional antiplatelet agent in patients who have detectable coronary artery aneurysms. Intravenous gammaglobulin in a dose of 400 mg/kg/day given daily for four days is of proved benefit in reducing the risks of coronary artery abnormalities.[39 40] A single dose of 2 g/kg given as a slow infusion over eight hours has recently been shown to be even more effective than the four dose regimen.[43] Immunoglobulin treatment is expensive and not completely without risks, and there continues to be a debate as to whether it should be reserved for a subgroup of patients with the most severe disease. How this group should be identified remains an unanswered question. Several adverse prognostic features have been recognised including prolonged fever, severe anaemia, hypoalbuminaemia, leucocytosis, and extreme thrombocytosis. None of these features is specific in identifying at risk patients and most authorities therefore currently advocate giving all patients with the disorder intravenous immunoglobulin.

In view of the long term risks of coronary artery thrombosis, patients with echocardiographically demonstrated abnormalities are usually treated with low dose aspirin for very prolonged periods of time, often for several years. Long term follow up of these patients is important. Finally, as with any relatively rare but serious disorder, elucidation of its aetiology, pathogenesis, and treatment is most likely to be achieved by widespread awareness of the disorder and by collaborative studies. Hopefully paediatricians in the UK will participate in further studies on this fascinating, but worrying paediatric disorder.

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Imaging in congenital deafness

One in every 1000 children has severe or profoundly severe hearing loss (greater than 50 dB hearing loss in the better hearing ear), which is detectable in the first year of life. In 90% the hearing loss is congenital and the causes are many and varied. A further one in 1000 has moderate to severe hearing loss and is not usually found until the age of 3 years.[1] Diagnosis and recognition of congenital hearing loss at the earliest possible age is essential, as is recognition of the type and degree of deafness. Any part of the hearing organ may be affected. There is a wide range of abnormalities due to arrested or abnormal development, the aetiology and pathogenesis of which is completely or partially understood in only a few cases. Children with conductive deafness can be judiciously selected for surgical correction involving a minimum of risk to normal structures if the anatomical deformities are carefully outlined.

Radiology can play a significant part in the management of the child with congenital deafness. Evaluation of the bony structures in the ear can be made with accuracy. Structural deformities of inner and middle ears frequently coexist to give both a conductive and sensorineural component to the deafness. In the inner ear, radiological evaluation of congenital deafness must assess inner ear structure related to probable cochlear function and identify those structural abnormalities which carry the risk of cerebrospinal fluid fistula. In the middle ear radiology must assess the feasibility of surgery for better sound conduction and the presence of any surgical hazards—for example, high jugular bulb, misplaced facial nerve, position of carotid artery—in addition to assessing structure and function in the favourable ear. Anatomical abnormality of the inner ear and middle ear are well recognised in association with the head and neck syndromes and at present imaging of the middle and inner ear is not routinely performed.

We suggest that patients should be selected for imaging in the following cases:

- In any syndrome known to be associated with structural deformity of the ear (see below).
- When there are certain spinal abnormalities present and including the Klippel-Feil syndrome.
- When there are abnormalities of the external ears including auricular appendages and pits.
- After attacks of meningitis and cerebrospinal fluid rhinorrhoea.

We believe that high resolution fine section computed tomography in the neonatal period is essential and that evoked response audiometry and tomography are complementary procedures.[2] Although screening tests would detect those infants with hearing impairment, imaging is the most important investigation particularly in those children for whom improvement is possible by surgical intervention.

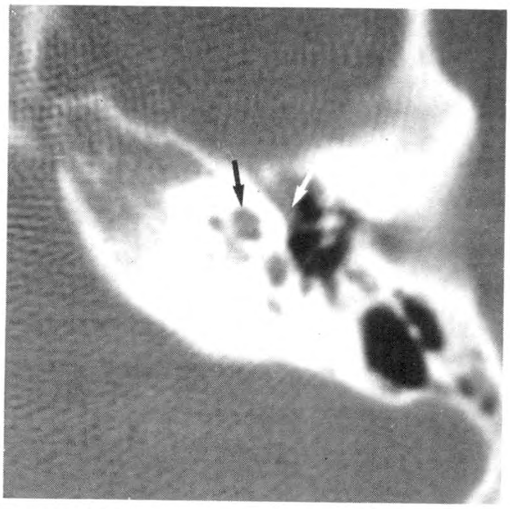
Severe cochlear abnormalities are incompatible with auditory function and therefore bilateral abnormalities imply that education must use methods not involving sound.

We perform high resolution fine section computed tomography using a Siemans DRH scanner and obtaining magnified 1 mm sections in axial and, when necessary, in coronal planes (fig 1). In order to reduce the radiation dose to the orbits to the minimum we recommend a plane at 30′ to the baseline, parallel with the roof of the orbit so that the globe is mostly below the sections. The dose to the cornea using this positioning is between only 0·9 and 1·8 millisieverts. We image our thin sections in the high resolution mode using a bone algorithm on a wide window setting of 3000 to 4000 Hounsfield units.[3]

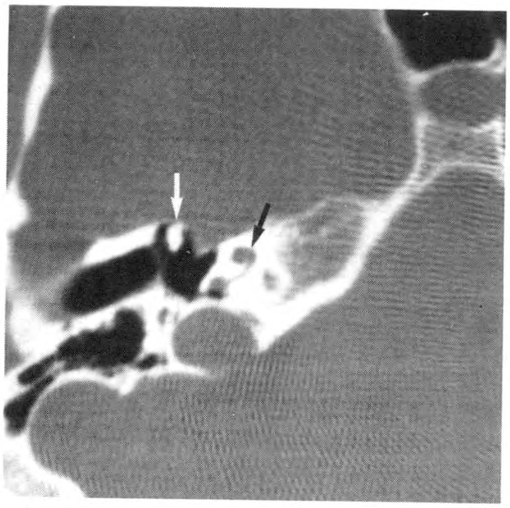
For all infants selected by our suggested guidelines we believe that high resolution fine section computed tomography should be the initial investigation, and it should be performed in the neonatal period when sedation is rarely required.

At present, classification of the underlying aetiology of hearing loss in the head and neck syndromes is difficult in view of our inadequate understanding of the pathogenesis.

Cochlear abnormalities are the most commonly observed malformation of the inherited disorders (fig 2). Of the congenital disorders, the otocraniofacial group of syndromes are among the most common and most important of those with malformations of the middle and external ears.



’igure 1 *Normal axial computed tomogram. Arrows point to distal coils of ochlea (black arrow) and tensor tympani (white arrow).*



igure 2 *Branchio-otorenal syndrome (earpits' deafness). Black arrow ints to small cochlea with two turns only. White arrow indicates ossicular ss attached to anterior attic wall.*

This group include craniofacial microsomia (Goldenhar's syndrome), mandibulofacial dysostosis (Treacher Collins syndrome), Pierre Robin syndrome, craniofacial dysostosis (Apert's syndrome, Pfeiffer's syndrome, Saethre-Chotzen syndrome, and Crouzon's syndrome), cryptophthalmos syndrome, Waardenburg's syndrome and branchio-otorenal syndrome.

The range of abnormalities of the middle and inner ear associated with these syndromes is wide. Thus some infants with Goldenhar's syndrome are found to have a narrow internal auditory meatus and a deficient labyrinth resulting in severe deafness while others with the same underlying syndrome have global hypoplasia of the structures in the middle ears including hypoplastic or absent ossicles.[4 5] There is considerable similarity between the abnormalities in the middle and inner ears in both hemifacial microsomia and mandibulofacial dysostosis.[6] Cochlear function is usually normal. Otopathology is less common in craniofacial dysostosis than in mandibulofacial dysostosis or hemifacial microsomia.[7] Ossicular malformation or fixation is reported in the craniofacial dysostoses.[8] These children also develop conductive deafness due to serous otitis media because of impaired eustachian tube function.[9]

Otopathology occurs less frequently with primary cervical shoulder anomalies than with craniofacial malformations. Sensorineural hearing loss is more common than conductive loss.[7] This group includes the Klippel-Feil syndrome and Wildervanck's syndrome, cleidocranial dysostosis, otocervical syndrome, and Sprengel's shoulder. Severe hearing loss occurs in up to 30% of children with the Klippel-Feil syndrome. A range of abnormalities may be demonstrated by imaging including gross labyrinthine deformities such as the Mondini defect—a deficiency of the central bony spiral of the cochlea which precludes normal hearing. In addition to these malformations of the inner ear, a variety of external and middle ear abnormalities occur.[10] Infants with Wildervanck's syndrome (the combination of Klippel-Feil and Duane's syndromes) may have a particularly severe combination of abnormalities. Ossicular malformation and atretic external auditory meati have been reported in infants with cleidocranial dysostosis, both abnormalities which are clearly demonstrated on high resolution fine section computed tomography.

The ostoskeletal syndromes (bone dysplasias) include osteogenesis imperfecta, dysplasias with increased bone density, Kniest's disease, otofacial digital syndrome type II (Mohr) and otopalatal digital syndrome. Hearing loss in these infants is frequently due to compression of the inner ear and foraminal narrowing. Congenital hearing loss is also found in some chromosomal abnormalities including trisomy 13–15, trisomy 18, trisomy 21, trisomy 22, and sex trisomy (Turner's syndrome) and in chromosomal deletion 4p- (Wolf-Hirschhorn syndrome). A combination of middle and inner ear abnormalities are reported.

Deafness occurs with endocrine disorders and, in particular, hypothyroidism. Structural abnormalities of the ear have, however, not been demonstrated and the hearing loss is usually reversed by appropriate hormone treatment. The one condition in which deformities of the bony labyrinth have been shown in association with endocrine disturbances is in infants with Pendred's syndrome who have severe hearing loss due to Mondini type defects with deficiency of the modiolus.

Many drugs produce hearing loss and tinnitus, usually from temporary or permanent damage to the cochlear end organ. Thalidomide produced structural abnormalities by a teratogenic effect in utero and ear abnormalities are the second most common result of thalidomide embryopathy with an estimated 10% of patients affected. The deformities have no characteristic or distinguishing feature. They do, however, tend to be bilateral, severe, and extensive and often involve external, middle, and inner ears.[11]

Deafness is a common feature of neurofibromatosis and is usually due to neuromas on the VIIIth nerve or bony dysplasia. The acronym CHARGE association is applied to that combination of congenital defects involving coloboma, heart disease, atresia of the nasal choanae, retarded development and/or central nervous system abnormalities, genital hypoplasia, and ear abnormalities. Computed tomography has demonstrated structural abnormalities in 50% in our series.[8] Atresia of the external auditory meatus, ossicular abnormalities, and cochlear deformities may be shown.

In some of the aforementioned conditions the hearing loss is static (for example, craniofacial microsomia) but in others, for example, the bony dysplasias it is usually progressive.

Computed tomography should be considered for any infant or child suspected of having one of these syndromes, although priority will obviously have to be given to more important defects of other systems.

We believe that in infants born with deformed pinna with or without external meatal atresia or with manifestations of one of the head and neck syndromes, imaging in the neonatal period should be performed, preferably before discharge home from the maternity unit. Examination at this stage has the following advantages:

- Sedation is rarely required.
- A full assessment of the middle and inner ears may be obtained with a few tomographic sections.
- The information obtained can be correlated with hearing assessments performed from 1–2 years of age.

The optimum age for imaging is difficult in those children in whom hearing loss is detected at a later age, particularly when the deficit is only detected at the age of 2–3 years when sedation is usually required. Severe labyrinthine deformities preclude any auditory function. Surgical attempts to improve sound conduction mechanism is rarely undertaken in unilateral malformations if the hearing in the other ear is normal.

Accurate knowledge of the structure of the inner and middle ears is essential from the earliest occasion possible, such that those infants in whom structural malformation precludes any hearing are detected and educated from the earliest age with methods not involving sound.

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ORIGINAL ARTICLES

Cranial magnetic resonance imaging in patients with tuberous sclerosis and normal intellect

David W Webb, J L G Thomson, J P Osborne

Abstract

The pattern of cerebral hamartomas among a population of patients with tuberous sclerosis and normal intellect was determined. All patients with tuberous sclerosis over 5 years old with normal intellect who were resident in the Bath health district were offered cranial scanning by magnetic resonance imaging. Cerebral axial and coronal images were obtained in 10 mm contiguous sections with a Picker 0·5 tesla magnetic resonance imaging unit. The number, size, and distribution of lesions found was recorded. Eleven of 13 eligible patients underwent scanning. Two patients had normal scans. Seven patients had between one and five subependymal nodules. Nine patients had between two and nine cerebral tubers best seen on T2 weighted images. Our findings suggest that the wrong conclusions may be drawn if the number of lesions alone is used to predict neurological outcome in tuberous sclerosis.

Tuberous sclerosis is an important cause of epileptic seizures and mental handicap in young children, and has an incidence of 1/6000 births.[1] The proportion of cases in whom these serious neurological sequelae develop is now believed to be lower than previously estimated.[2] Mental handicap usually occurs in children who suffer seizures in the first year of life. Among children with a history of early seizures it is very difficult to predict neurological outcome. Most will develop mental handicap and many have resistant seizures but a few develop normally with or without a continuation of seizures. It has been suggested that the number of lesions identified on cranial magnetic resonance imaging (MRI) may predict mental development.[3 4]

Cerebral involvement in tuberous sclerosis is characterised by subependymal glial nodules, cortical and subcortical tubers, and giant cell astrocytomas. The relationship between the number of cerebral hamartomas and the clinical course has been examined. One large study of cranial computed tomography in children with tuberous sclerosis found little relationship between mental development and the incidence of subependymal glial nodules or of cortical and white matter lesions.[5] Magnetic resonance imaging appears to be more sensitive than computed tomography in detecting parenchymal tubers,[6] which may be more prone to cause seizures. Lesions with high signal intensity on images with long repetition times are characteristic (T2 images). The size and configuration of the signal abnormalities on cranial MRI have been found to correlate exactly with the pathological findings seen grossly and microscopically. The MRI findings appear to be less affected by age than are the corresponding low attenuation changes seen on computed tomography.[7]

There is very little information about the pattern of cerebral lesions in tuberous sclerosis patients with normal intellect, and the pattern in patients with no history of seizures has not been documented. We present the cranial MRI findings in a population of patients with tuberous sclerosis with normal intellect, some of whom were free of seizures.

Subjects and methods

POPULATION

Twenty two individuals known to be affected by tuberous sclerosis and resident in the Bath health district were previously ascertained for a prevalence study.[1] After an interview by the authors and a review of their academic, social, and (for adults), work history, 13 of these patients were identified as over 5 years old and not mentally handicapped. They were able to read and write, to make normal progress at school, and the adults were capable of gainful employment.[2] Eleven consented to cranial MRI. One patient was an obligate gene carrier with no clinical evidence of the disease[8] but all the other patients fulfilled diagnostic criteria outlined by Gomez.[9] Eight patients had no history of seizures. Two girls aged 6 and 8 years had both recently developed partial seizures with secondary generalisation and were free of seizures on antiepileptic medication; both girls were doing well in normal schools. One woman aged 38 had occasional nocturnal seizures which began when she was 19 years old and for which she had refused treatment. She had a part time responsible job and could read and write. The two patients not consenting to MRI scan were a girl of 12 years with a hemiplegia and generalised seizures and a woman of 35 years also with a history of generalised seizures.

METHODS

Ethical approval was obtained from the local ethical committee and informed consent received before the study from the patients or their parents. Images were obtained on a Picker magnetic resonance imaging unit with a 0·5 tesla magnetic field. Multiecho sequences were taken in axial section with a repetition time of 1800 ms and an echo time of 30 and 100 ms; and inversion recovery sequences in coronal section with a repetition time of 1500 ms, an echo time

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of 26 ms, and an inversion time of 500 ms. Axial scans consisted of 16 contiguous 10 mm slices, and coronal scans of eight contiguous 10 mm slices. Although the minimum resolution of the imaging unit is 2 mm, it is difficult to interpret lesions less than 4 mm in size. Therefore to avoid misinterpretation and allow comparison in future studies, the number, size, and distribution of lesions measuring more than 4 mm in greatest diameter were recorded. Lesions present in the same area on two contiguous scans were counted as one.

Results

Two patients had normal scans. Seven patients had between one and five subependymal glial nodules. Nine patients had between two and nine cerebral tubers. Three patients had some ventriculomegaly.

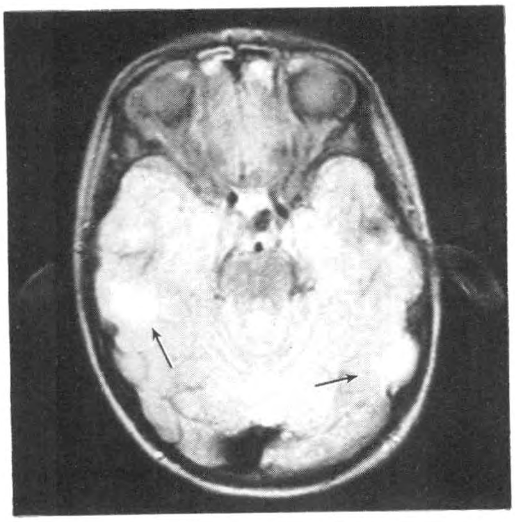
Tubers occurred in all cerebral lobes, although most frequently in the frontal and parietal lobes (table). One patient had a cerebellar tuber. Most tubers (36/44) were less than 1·5 cm in greatest diameter and were frequently subcortical rather than cortical. Six lesions were in the deep white matter. Six of the patients each had between one and three other possible abnormal areas measuring less than 4 mm. These were all within the deep white matter and were not included for analysis. Tubers were most easily seen on T2 weighted images where they appeared as areas of increased signal intensity (figure). Corresponding abnormalities on T1 weighted images usually appeared hypointense.

Tubers measuring 1·5 cm or greater were only seen in children. One girl aged 8 years had four tubers larger than 1·5 cm in size. This child is top of her class at school and has an Edinburgh reading age of 11 years. Another girl aged 13, with no history of seizures, was in the first 10 of her class for mathematics, English, and science and had three lesions 1·5 cm or larger.

Distribution of cerebral lesions on cranial MRI of patients with tuberous sclerosis and normal intellect

Age (years)	*Frontal*		*Parietal*		*Occipital*		*Temporal*		*No of subependymal glial nodules*
	Right	*Left*	*Right*	*Left*	*Right*	*Left*	*Right*	*Left*	
6*	2	1	2						5
8*	1	1	1	1	1	2	1	1	5
13	1		2	3		2			4
17		2	1	1					0
21									0
25	4								0
38	1		1	2					2
38*			2		1			1	4
45									0
51	1	1		1					1
78			1			1			2

*History of seizures.



T2 weighted axial cranial MRI scan showing two hyperintense cerebral tubers.

Discussion

It is our experience that individuals who reach 5 years of age with normal development do not develop mental handicap from tuberous sclerosis and for this reason our patients are very unlikely to do so. The cranial MRI findings in patients with tuberous sclerosis with mental handicap and poorly controlled seizures is well documented.[6] We have found similar lesions in a population of tuberous sclerosis patients with normal intellect, the majority of whom had no history of seizures.

We believe we have accurately identified hamartomas of at least 4 mm in size and that the number of cerebral lesions we found is sufficient to make cranial MRI unlikely to be a reliable predictor of clinical outcome. It is possible that the distribution and size of lesions may be of greater help. Both patients with temporal lobe lesions had seizures. We found very few occipital hamartomas and two of the four patients with occipital lesions had seizures. One study has suggested that abnormalities in this lobe correlate best with repeated interictal electroencephalogram abnormalities.[10] We did not find that bilateral lobe involvement was associated with a poor prognosis. A small number of tubers in our study measured more than 1·5 cm and only three were greater than 2 cm. One previous report found many lesions more than 3 cm but size had not otherwise previously been mentioned.[11]

We accept that none of our patients had more than 10 cortical lesions but it would seem unwise to extrapolate that this would never occur in affected individuals with normal intellect. One of our patients, who is a bright student, had nine cerebral tubers. Others have reported severely mentally handicapped patients with considerably fewer lesions.

Some individuals may have an inherently higher seizure threshold which protects them from developing seizures at an early age despite multiple large or strategically located lesions. Neuronal heterotopias thought to represent neuronal arrest have been described in areas of the brain unaffected by cerebral tubers or subependymal glial nodules.[9] These may be below the resolution of MRI imaging and their contribution to increased seizure potential or impaired cognitive function are unknown.

We have found that the cranial abnormalities in older patients were smaller, more frequently subcortical rather than cortical, and more difficult to identify. The cerebral lesions in tuberous sclerosis may become less obvious on MRI with advancing age as is the case for lesions seen on cranial computed tomography.[7]

Our findings suggest that the wrong conclusions may be drawn if the number of lesions alone on cranial MRI is used to predict neurological outcome in tuberous sclerosis. Our results provide a basis for comparison in future studies and we would recommend that both the number, size, and distribution of lesions should be recorded.

This paper was presented at the Paediatric Research Society meeting, University of Manchester, 6 April 1991.

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IgG subclass specific antibody response in recurrent bronchitis

F de Baets, R Pauwels, I Schramme, J Leroy

Abstract

The IgG subclass specific immune response against pneumococcal type 3 polysaccharide antigen before and after immunisation in healthy children and children with recurrent bronchitis was studied. Recurrent bronchitis was defined as three or more episodes a year, during at least two consecutive years, of bronchopulmonary infection, productive cough with or without fever, and/or diffuse rales by physical examination. Twenty five patients and 15 healthy children were selected.

The patient group had lower concentrations of IgG_1 and IgG_2 specific pneumococcal antibodies compared with healthy children, regardless of whether or not the total IgG_2 concentration was low. The children with recurrent bronchitis showed a greater increase in IgG_1 and IgG_2 antibodies after immunisation than the controls.

It is concluded that children with recurrent bronchitis show a decreased humoral immune response to pneumococcal type 3 polysaccharide antigen. This finding suggests that a defect in the humoral immune response against polysaccharide antigens is an important cause of recurrent bronchitis in childhood.

A high incidence of IgG_2 subclass deficiency is reported in children with recurrent upper and lower respiratory tract infections.[1–6] Antibodies against polysaccharide antigens are mainly found in the IgG_2 subclass.[7–10] Polysaccharide antigens are the main antigenic determinants of encapsulated bacteria such as *Haemophilus influenzae* and *Streptococcus pneumoniae*; the latter is a major cause of recurrent respiratory infections. In IgG_2 deficient children, the humoral immune response after immunisation with a polysaccharide antigen is significantly decreased.[11–14] Ambrosino *et al* reported a patient with recurrent bacterial pneumonia, normal concentrations of immunoglobulin classes and subclasses, but a significantly decreased immune response against polysaccharide antigens.[15] This suggested a functional disorder in humoral immunity. Recently some authors observed a decreased antibody response after immunisation with a polysaccharide antigen in children with recurrent infections without any immunoglobulin class or subclass deficiency.[16–18] Therefore we were interested in the serum concentrations of IgG subclass specific antibodies against type 3 polysaccharide antigen before and after immunisation in children with recurrent bronchitis.

Patients and methods

PATIENTS

Because a formal definition of recurrent bronchitis in childhood is lacking, we defined it as three or more episodes a year, during at least two consecutive years, of bronchopulmonary infection, productive cough with or without fever, and/or diffuse rales by physical examination. In order to avoid the inclusion of mainly asthmatic patients, wheezy or dyspnoeic children were excluded and children had to be at least 3 years old. Asthma as the aetiological factor in recurrent respiratory symptoms is usually recognised clinically by 3 years.[19]

According to this definition 25 children (15 boys) (mean age 57 months, range 36–105) were selected. Thirteen patients were attending the outpatient department of the paediatric respiratory clinic at the University Hospital, Ghent; 12 were residents in an asthma centre at De Haan, Belgium.

Respiratory symptoms were first seen at the mean age of 7 months. The mean annual rate of episodes of respiratory symptoms was 10. In 84% of the children, fever was a constant sign during symptom episodes. Sixty percent of the patients had recurrent pneumonia and in 72% there was no seasonal occurrence of symptoms. There was a family history of chronic bronchitis in a first degree relative in 36% of the children, with atopy and/or asthma in 56%. There was a combination of both chronic bronchitis and asthma in more than one first degree relative in 12%. Adenoids and tonsils were removed in 48% and 28% of the patients respectively.

In 40% of the patients total IgE serum concentrations were higher than 2 SD above the mean for age.[20] Eight percent showed one or more positive radioallergosorbent tests. Sweat tests gave negative results in all children. Ciliary function was examined on bronchial biopsy specimens or nasal swabs in 15 children. The immotile cilia syndrome was diagnosed in one patient. Gastro-oesophageal reflux was found in four of the 15 children tested. Forty eight percent of the patients showed persistent abnormalities on radiographs of the thorax. Persisting radiological signs consisted of atelectasis or infiltration of the right middle lobe and/or lingula. Bronchoscopy was performed in 12 children and *H influenzae* was cultured from bronchoalveolar lavage fluid in two patients. Severe signs of chronic bronchitis were found in all of the patients (that is, hypersecretion, pale mucosae, hypertrophic submucosal glands, longitudinal mucosal folds). Six of the nine children in whom a bronchography was done showed bronchiectasis.

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A control group of 15 children, mean age 71 months (range 36–144), was enrolled. The parents of 640 children in an infant and elementary school were informed of the study and asked for their cooperation. All control children were selected after they had returned a questionnaire in which the proneness to upper and lower respiratory tract infection was evaluated. Only children with two or fewer yearly episodes of bronchitis, rhinitis, sinusitis, or otitis were accepted. Children with a history of pneumonia or any infectious disease within one month before the start of the study were excluded. No significant difference in mean age between groups was observed (Student's *t* test).

Patients and control children were immunised with a pneumococcal vaccine (Pneumovax 23, Merck Sharp and Dohme). Serum samples were taken before and one month after immunisation.

METHODS

IgG subclasses were measured by enzyme linked immunosorbent assay (ELISA) using monoclonal antibodies. The latter were obtained from the Binding Site Limited (Birmingham). The specificity of these monoclonal antibodies was tested as reported by Jefferis and Reimer.[21] Each serum sample was studied twice and a sample from a normal serum pool was included in every assay plate. A standard curve was constructed for each subclass using a reference preparation supplied by the World Health Organisation (SPSO1). The intra-assay coefficient of variation was 7%, 5%, 4%, and 7% for IgG$_1$, IgG$_2$, IgG$_3$, and IgG$_4$ respectively. The interassay coefficient of variation was 13%, 12%, 18%, and 15% for IgG$_1$, IgG$_2$, IgG$_3$, and IgG$_4$ respectively. Our own reference values for IgG subclasses in different age groups are given in table 1. Sera were obtained from 175 healthy children aged 0 to 18 years at the time of visiting the paediatric outpatient department for non-infectious or non-inflammatory diseases or when they were admitted for elective surgery. All control children were selected after they had answered a questionnaire in which the proneness to upper and lower respiratory tract infection was evaluated as mentioned above. If C reactive protein concentration was greater than 10 000 μg/l or α_2 globulin was higher than 0·9 g/l the serum sample was omitted as a control. As immunoglobulin concentrations are not distributed normally, geometric means and normal ranges of the concentrations for each subclass were calculated for each age group from the logarithm of the experimental values.[22] Total serum immunoglobulins were measured by nephelometry. Patients were considered deficient for an immunoglobulin class or an IgG subclass if they had values more than 2 SD below the geometric mean for age matched healthy subjects. Total IgE and specific IgE were measured by radioimmunoassay. Ciliary function was examined on bronchial biopsy specimens or nasal swabs in the laboratory of Dr S van der Baan, Amsterdam, The Netherlands.[23] Sweat chloride was measured by the method of Gibson and Cooke.[24] Gastro-oesophageal reflux was evaluated by the Tuttle test.[25]

Table 1 Reference values for IgG subclasses in different age groups. Values are mean (range:mean and 2 SD) in g/l

Age (years)	*IgG$_1$*	*IgG$_2$*	*IgG$_3$*	*IgG$_4$*
0–0·5 (n=13)	2·35 (0·85–6·50)	1·08 (0·13–8·73)	0·18 (0·03–0·93)	0·11 (0·02–0·58)
>0·5–1 (n=10)	4·05 (1·43–11·49)	0·73 (0·22–2·46)	0·35 (0·11–1·10)	0·05 (0·01–0·19)
>1–<3 (n=17)	3·50 (1·54–7·94)	0·88 (0·36–2·17)	0·33 (0·10–1·12)	0·06 (0·02–0·39)
3–<5 (n=21)	5·74 (2·23–14·78)	1·44 (0·51–4·09)	0·38 (0·10–1·43)	0·25 (0·05–0·14)
5–<7 (n=22)	6·44 (2·02–21·67)	1·48 (0·46–4·77)	0·42 (0·13–1·35)	0·34 (0·05–2·12)
7–<10 (n=35)	6·52 (2·73–15·56)	1·51 (0·49–4·66)	0·42 (0·14–1·23)	0·24 (0·03–1·99)
10–<13 (n=23)	5·68 (3·08–9·22)	1·88 (0·69–5·13)	0·44 (0·16–1·20)	0·23 (0·02–2·49)
13–<17 (n=26)	6·24 (3·40–11·11)	3·09 (0·95–9·98)	0·55 (0·27–1·14)	0·20 (0·02–2·52)
≥17 (n=8)	6·01 (3·57–10·11)	4·60 (1·23–17·10)	0·54 (0·23–1·25)	0·20 (0·03–1·10)

Subclass specific pneumococcal antibodies were measured by ELISA. Microtitre plates (Nunc, Maxisorp) were coated with 0·1 ml of type 3 pneumococcal polysaccharide (American Type Culture Collection), 10 μg/ml, dissolved in a barbital buffer, diluted 1:100 in distilled water. The plates were incubated for 96 hours at 37°C and kept at 4°C until used. A standard curve for different IgG subclasses was formed with a standard serum (Janssen Biochemico, Belgium). Dilutions 1/100, 1/200, 1/400, 1/800, 1/2000, 1/4000, 1/8000, 1/10 000, and a blank for IgG$_1$ and dilutions 1/10, 1/20, 1/40, 1/80, 1/200, 1/400, 1/800, 1/1000, and a blank for IgG$_2$, IgG$_3$, and IgG$_4$ were obtained. Serum samples of patients and controls were diluted 1/200, 1/500, and 1/1000 for IgG$_1$ and 1/40 and 1/80 for IgG$_2$, IgG$_3$, and IgG$_4$ antibodies. After washing, microtitre plates were incubated with serum samples and standard samples 0·1 ml for three hours at 37°C.

Subclass specific pneumococcal antibodies were measured with monoclonal subclass specific antibodies (Janssen). These monoclonal antibodies were conjugated with horseradish peroxidase. The conjugate was diluted 1/2500 for IgG$_1$, 1/500 for IgG$_2$ and IgG$_3$, and 1/250 for IgG$_4$. After washing, diluted conjugate was added to the microtitre plates and incubated for two hours at room temperature. Microtitre plates were washed five times and 0·1 ml substrate was added. After 30 minutes of incubation at room temperature the reaction was stopped by 0·05 ml of 2 M sulphuric acid. The extinction coefficient was read on an ELISA reader at 492 nm. As well as a standard curve for subclass specific pneumococcal antibodies, a standard curve for the specific IgG subclass tested was also obtained in every plate. For IgG$_1$ dilutions 1/5000 to 1/320 000 and for IgG$_2$, IgG$_3$, and IgG$_4$ 1/100 to 1/10 000 were used. Extinction coefficients measured for subclass specific antibodies were also read on the simultaneous measured standard curve for the specific IgG subclass. After adjusting for the dilutions used a quantitative value for the specific pneumococcal antibodies could be obtained.

The interassay coefficient of variation for IgG subclass specific pneumococcal antibodies was 12%, 15%, and 15% for IgG$_1$, IgG$_2$, and IgG$_4$

Table 2 Mean IgG subclass specific antibody concentrations against pneumococcal polysaccharide type 3 antigen before and after immunisation. Values are mean (2·5–97·5 centiles) in µg/ml

	(A) Control group (n=15)			*(B) Patient group (n=25)*			*(C) Patient group (not IgG_2 deficient) (n=20)*			*p Values*	
										(A) v (B)	*(A) v (C)*
IgG_1											
Before	38·5 (1[illegible]·5–73·5)	0·8*	0·74†	23·7 (7·4–63·0)	0·004*	0·002†	23·8 (7·6–92·3)	0·003*	0·002†	0·008	0·006
After	38·7 (1[illegible]·0–72·5)			34·6 (9·2–109·0)			33·7 (9·1–130·0)			0·08	0·07
IgG_2											
Before	51·1 (5·0–260·0)	0·06*		15·7 (5·0–53·6)	0·003*		14·8 (5·0–60·0)	0·003*		0·002	0·003
After	60·5 (7·3–210·0)			29·9 (5·0–86·0)			26·8 (5·0–76·5)			0·01	0·02

*p Values between before and after immunisation for both IgG subclasses.
†p Values between IgG_1 and IgG_2 before immunisation.

respectively. No measurable concentrations of IgG_3 specific pneumococcal antibodies were found.

The significance of differences between groups was determined with the unpaired non-parametric Mann-Whitney U test. Significance of increases in antibody titres after immunisation was evaluated by the paired non-parametric Mann-Whitney U test.

Results

Two of the 25 patients (8%) had a decreased serum concentration for IgG and four (16%) had IgA deficiency. IgG subclass deficiency was found in 17 (68%) of the patients with recurrent bronchitis: two (8%), four (16%), and seven (28%) for IgG_2, IgG_3, and IgG_4 respectively, two (8%) for IgG_2 and IgG_4, one (4%) for IgG_3 and IgG_4, and one for IgG_2, IgG_3, and IgG_4. No immunoglobulin class or subclass deficiency was found in the healthy control group.

The mean and range of serum antibody concentrations against pneumococcal polysaccharide antigen type 3 in the IgG_1 and IgG_2 subclass before and after immunisation in patients with recurrent bronchitis, healthy control children, and patients with normal IgG_2 concentrations with recurrent bronchitis are shown in table 2.

Patients with recurrent bronchitis, regardless of whether or not there was an IgG_2 deficiency, had lower concentrations of IgG_1 and IgG_2 specific antibody than the controls. Antibody concentrations before immunisation in the group with recurrent bronchitis were significantly higher for IgG_1 than for IgG_2. In the control group antibodies before immunisation were higher in the IgG_2 subclass, although this was not significant.

Both patient groups showed a greater increase in IgG_1 and IgG_2 specific antibodies after immunisation than the controls. A 1·9 ($p<0·003$) and 1·2 ($p<0·06$) fold increase in IgG_2 specific type 3 pneumococcal antibodies was seen after immunisation in the patient (group B) and control group respectively. The mean concentration of IgG_2 subclass specific pneumococcal antibodies after immunisation in the patients with recurrent bronchitis remained significantly lower than the mean concentration after immunisation in the control group.

No specific type 3 pneumococcal polysaccharide antibodies were detected in the IgG_3 subclass. In some children a low value of specific pneumococcal antibodies was seen in the IgG_4 subclass; immunisation did not provoke detectable changes.

Discussion

Before immunisation antibodies against type 3 pneumococcal polysaccharide antigen in control children were mainly of the IgG_2 subclass; this is in contrast to those with recurrent bronchitis who had mainly IgG_1 subclass antibodies. However, antibody concentrations before immunisation in both the IgG_1 and IgG_2 subclass were significantly lower in the group with recurrent bronchitis. In view of the frequent respiratory infections, one would expect a higher antibody concentration in these children. This strongly suggests a primary defect in the humoral immune response in these children.

It is already known that IgG_2 deficient children have a decreased immune response against polysaccharide antigens.[11–14] By omitting IgG_2 deficient children, we still find a significant difference, suggesting a decreased humoral immune response against pneumococcal polysaccharide antigen in a potentially larger group of children with recurrent bronchitis and normal serum IgG_2 concentrations.

These findings are in general accordance with the results of Freijd *et al.*[9] They reported significantly lower concentrations of IgG_1 and IgG_2 specific type 6a pneumococcal antibodies in a group of 15 children with recurrent otitis media compared with control children and healthy adults. In their patient group, specific pneumococcal antibody concentrations were higher in the IgG_1 than in the IgG_2 subclass, but a similar pattern was also seen in their control group. However, in 15 healthy adults specific pneumococcal antibody concentrations were higher in the IgG_2 subclass. Their control group was younger than our control children and were selected from an ear, nose, and throat clinic if they had suffered from one or two episodes of otitis media. It could be argued that their control group contained antibody deficient patients. Our results are in accordance with those of Barrett *et al*[10] and Schatz and Barrett[26] who showed that antibodies against polysaccharide antigens in healthy children over the age of 3 years are mainly of the IgG_2 subclass.

The relatively small increase in pneumococcal antibodies after immunisation in both the control and patient group confirms the findings of Douglas *et al* who reported a poor antibody response after pneumococcal vaccine up to the age of 5 years.[27] Paton *et al* reported a 2·1 to 2·9 fold increase in type 3 pneumococcal antibodies after immunisation in children aged 5 to 15 years.[28] Barrett *et al* observed a threefold increase in IgG_2 type 3 specific pneumococcal antibodies after immunisation in adults.[10] These observations suggest an increasing immune reactivity against pneumococcal vaccine with age.

The reason why patients show a greater rise in antibodies after immunisation, compared with controls, is not entirely clear. It might be explained in part by complexing of antibodies with injected antigens, thus reducing the amount of antigen available to stimulate B lymphocytes. This idea is supported by the finding that in the control group, the four children with a low initial concentration of IgG_2 specific pneumococcal antibodies (<10 μg/ml) showed a mean 4·2 fold increase after immunisation.

Ambrosino *et al* found no significant difference in serum concentrations of IgG specific pneumococcal antibodies after immunisation between a group of respiratory infection prone children and controls.[13] Perhaps differences were not obvious because total IgG was studied instead of IgG subclass specific responses.

No significant differences were observed in antibodies before and after immunisation in subgroups of patients with gastro-oesophageal reflux or high IgE concentrations compared with the whole group. The two IgG deficient patients showed both low antibody concentrations before immunisation (<5 μg/ml); in one there was an excellent and in the other no immune response after immunisation. Two of the four IgA deficient children had a good immune response after immunisation and three of them showed low antibody concentrations before immunisation.

IgG subclass measurements are considered important diagnostic tests in children with unexplained recurrent bronchitis. However, measurement of IgG subclass specific polysaccharide antibody concentrations before and after immunisation, compared with controls, is a more sensitive test to detect an antibody deficiency against polysaccharide antigens. Because of the relatively small antibody increase after immunisation with a pneumococcal vaccine, even in healthy children, immunisation with a *H influenzae* type b vaccine may be preferable. Other investigators using this vaccine observed a definite increase in specific antibody concentrations in control children compared with infection prone patients.[17]

Although recurrent respiratory symptoms are a common problem in preschool children, most are due to increased non-specific bronchial hyper-reactivity evoked or increased by recurrent viral infections. In these children symptoms can be controlled by antiasthmatic drugs. However, in a small group of patients recurrent bacterial respiratory infections are suspected on a clinical, radiological, and serological basis. Our 25 patients were selected over a three year period from a tertiary paediatric reference centre and an asthma centre with 250 patients from all over Belgium. Although such children are frequently seen in specialised paediatric respiratory clinics, their prevalence in the population is relatively low.

As suspected in some children with IgG subclass deficiency,[29] [30] most of the patients in our study may have retarded development (immaturity) of the humoral immune system and repeat immunisation with polysaccharide antigens will be necessary to confirm a true deficiency. Prophylactic treatment with antibiotics or regular gammaglobulin replacement treatment may decrease respiratory symptoms and prevent serious pulmonary disease. However, controlled clinical trials will be necessary to confirm these possible benefits.

In conclusion, children with recurrent bronchitis show a decreased humoral immune response against pneumococcal type 3 polysaccharide antigen. This finding suggests that a defect in the humoral immune response against polysaccharide antigens is an important cause of recurrent bronchitis in childhood.

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Kawasaki or not Kawasaki

As there is no diagnostic test for Kawasaki disease the diagnosis must be made on clinical findings and the exclusion of other diseases. In my pocket notebook I carry the following list taken from the *New England Journal of Medicine* (1986;**315**:388):

(1) Fever lasting at least five days plus four of:
  (a) bilateral conjunctival injection
  (b) red throat, or fissured lips, or strawberry tongue
  (c) peripheral erythema, peripheral oedema, periungual desquamation, or generalised desquamation
  (d) truncal rash
  (e) cervical glands
(2) No other explanation.

In a multicentre study in the United States (Jane C Burns and colleagues, *J Pediatr* 1991;**118**:680–6) the clinical features were compared of 280 children with Kawasaki disease and 42 who had been referred because of a suspicion of that diagnosis but turned out to have something else. The something else was measles in 12 cases, a presumed but unidentified viral infection in another 12, a drug reaction in six, and group A β haemolytic streptococcal infection in five. Of the other six children one each had juvenile chronic arthritis, a presumed bacterial cervical adenitis, and infection with adenovirus, influenza A virus, Epstein-Barr virus, and *Leptospira interrogans*.

The following findings occurred in a small minority of patients with Kawasaki disease and were significantly more common in the non-Kawasaki disease patients: conjunctival exudate, discrete lesions inside the mouth, exudative pharyngitis, and generalised lymphadenopathy. Several features were found more often in Kawasaki disease to a very high degree of statistical significance ($p \leq 0{\cdot}001$). They were injected bulbar conjunctivae, red or cracked lips, strawberry tongue, and perineal rash. This, however, is an excellent example of the distinction between statistical significance and clinical usefulness. Red lips, for instance, were found in 94% of cases of Kawasaki disease and 64% of the others. The difference is statistically very significant ($p < 0{\cdot}001$) but as a single piece of clinical information it is clearly useless for diagnostic purposes. What we need to know about any diagnostic procedure, either laboratory or clinical, is its sensitivity and specificity. The clinical features with a high sensitivity in the diagnosis of Kawasaki disease all seem to have a low specificity when taken as isolated findings. Perhaps certain combinations of features would be more specific but unfortunately these authors have not provided us with that information. Their conclusion is that the clinical criteria for the diagnosis of Kawasaki disease are unreliable. The diagnosis is made by using the specified clinical criteria and excluding other conditions but the decision to treat with immunoglobulin may have to be taken on the basis of an uncertain diagnosis.

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Ultrathin flexible bronchoscopy in neonatal intensive care units

Jacques de Blic, Christophe Delacourt, Pierre Scheinmann

Abstract

Thirty seven flexible bronchoscopies were performed in 33 infants in a neonatal intensive care unit, using a 2·2 mm flexible ultrathin bronchoscope. Twenty eight procedures were performed via an endotracheal tube or tracheostomy and nine in spontaneously breathing infants. Indications for endoscopy included persistent atelectasis and/or emphysema (n=21), unexplained acute respiratory distress (n=10), stridor (n=3), assessment of congenital abnormalities of the tracheobronchial tree (n=2), and follow up of an endobronchial granuloma during the course of corticosteroid treatment (n=1). Abnormal airway dynamics and/or abnormal structure were seen in 23 of 37 cases. In 54% of the procedures, the results of bronchoscopy had a direct effect on further management. The procedure was well tolerated and completed in less than two minutes. Our results suggest that the ultrathin flexible bronchoscope improves airway exploration and the understanding of respiratory disorders during the first months of life, particularly in ventilated infants.

Persistent lung atelectasis, localised hyperinflation, and acute respiratory failure are common events in neonatal intensive care units (NICU). They constitute well accepted indications for urgent bronchoscopy.[1] Direct examination of the airways is the definitive diagnostic procedure in infants with bronchopulmonary dysplasia,[2] congenital heart and/or lung anomalies,[3 4] and generally in intubated mechanically ventilated infants. Because of the small internal diameter of the airways and/or of the endotracheal tube ultrathin flexible bronchoscopes have been developed.[5–8] Valuable information is thus provided concerning patency and the position of the endotracheal tube[5 8 9] and in evaluating tracheal injury.[10] This report describes our experience with an Olympus 2·2 mm flexible bronchoscope in the assessment of airway obstruction by malacia, intrinsic obstacles, or extrinsic masses or vessels.

Patients and methods

Between October 1989 and April 1990, we performed 37 flexible bronchoscopies in 33 infants. The mean age at presentation was 94 days (range 2 days to 9 months) and the mean weight 4 kg (range 1010–7000 g).

Twenty seven infants had an underlying disease: bronchopulmonary dysplasia (n=9), congenital heart disease (n=10), congenital malformation of the lower respiratory tract (n=6) including scimitar syndrome, pulmonary artery 'sling', bronchopulmonary sequestration, left diaphragmatic hernia with pulmonary hypoplasia, and two infants with tracheo-oesophageal fistula with oesophageal atresia; one child had bullous epidermolysis and one had cystic fibrosis. The remaining six children ranged in age from 6 to 22 days and had been admitted to the NICU for the sole diagnosis of neonatal respiratory distress.

Flexible bronchoscopy was performed with a prototype flexible ultrathin bronchoscope with an outer diameter of 2·2 mm (model XBF22 Olympus Corporation). This bronchoscope is immersible, it has an angle of flexion of 130° and an angle of antiflexion of 65°, but no suction channel.

Twenty six of the 37 endoscopies were carried out in intubated children. The diameters of the endotracheal tubes were as follows: 2·5 mm (n=4), 3 mm (n=11), 3·5 mm (n=9), and 4 mm (n=4). The flexible bronchoscope was passed through a swivel Y connector (Vigon, France) located between the endotracheal tube and the ventilator. The adaptor is specially fitted with a cleft to accommodate the bronchoscope and thus allows uninterrupted mechanical ventilation and oxygen delivery. In two cases the bronchoscope was passed through a tracheostomy stoma. No sedation was used before the procedure. All bronchoscopies were performed after preoxygenation in order to obtain an arterial oxygen saturation (SaO_2) greater than 90%. Except for changes in fractional inspired oxygen, ventilator settings remained unchanged during the procedure.

Nine infants were ventilating spontaneously but their weight (<2500 g) and/or their respiratory status precluded the use of a conventional paediatric flexible broncoscope (external diameter 3·6 mm). Bronchoscopies were performed transnasally with an ultrathin flexible bronchoscope, according to the technique used in older children,[11] with sedation and topical anaesthesia of upper airways with lignocaine. Special care was taken to apply suction carefully to the upper airways as the instrument has no operator channel. The cross section of the XBF22 is approximately one third that of the paediatric bronchofibrescope (3·8 mm^2 *v* 10 mm^2), thus allowing sufficient spontaneous ventilation, even in low birthweight neonates. All flexible bronchoscopies were performed in the NICU. Heart rate and oxygen saturation (Ohmeda), were continuously monitored in all patients during the procedures.

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Indications and findings of 37 ultrathin flexible bronchoscopies in a NICU

Indications	*No of cases*	*Findings*
Persistent atelectasis/emphysema	21	Normal (n=2), granuloma (n=2), inflammatory stenosis (n=3), bronchomalacia (n=5), vascular compression (n=5), foreign body (n=1), hypersecretion (n=3), tracheal bronchus (n=2)*
Acute respiratory distress	10	Normal (n=5), granuloma (n=1), bronchomalacia (n=2), tracheomalacia (n=1), hypersecretion (n=1)†
Stridor	3	Tracheomalacia (n=1), bronchomalacia (n=1), laryngeal bulla (n=1)
Congenital abnormalities of tracheobronchial tree‡	2	Normal (n=1), vascular compression (n=1)
Control	1	Normal (n=1)

*Associated tracheomalacia in one case and inflammatory stenosis of the right intermediate bronchus in the other case.
†Airway examination impossible.
‡Isolated (without atelectasis or emphysema) pulmonary sequestration and pulmonary artery 'sling'.

Indications for endoscopic examination (see table) included the suspicion or assessment of obstacles caused by vascular compression in children with congenital heart-vessel abnormalities or by stenosis, granuloma, or tracheobronchomalacia in long term mechanically ventilated infants. Most procedures were carried out secondary to persistent atelectasis and/or emphysema (n=21) or in instances of unexplained acute respiratory distress (n=10). Other indications for ultrathin bronchoscopy included stridor (n=3), assessment of congenital abnormalities of the tracheobronchial tree (n=2), and follow up of an endobronchial granuloma during the course of corticosteroid treatment (n=1). In seven cases flexible bronchoscopy was performed in the early postoperative period: after cardiac surgery (n=5) and after repair of the left diaphragmatic hernia (n=1) and of an oesophageal atresia (n=1).

Results

In 9/37 cases flexible bronchoscopy excluded suspected extrinsic or intrinsic obstruction of the airways (see table). The bronchoscopy confirmed laryngeal lesions in a 2 month old infant with bullous epidermolysis.

On four occasions massive bronchial hypersecretion was documented. In one case, vision was so blurred that airway examination was impossible. In another case, a mucous plug located in the intermediate bronchus had to be subsequently removed with a rigid bronchoscope.

In 23 of 37 cases, abnormal airway dynamics and/or abnormal structure were seen. Severe tracheomalacia and/or bronchomalacia were observed on 10 occasions (bronchopulmonary dysplasia in three, congenital heart anomalies in four, scimitar syndrome in two, and after tracheo-oesophageal fistula remain in one). Airway compression by enlarged heart cavities or vessels was found in five cases of congenital heart anomalies and in the case of pulmonary artery 'sling'. Using ultrathin bronchoscopy we documented three cases of inflammatory stenosis of the right intermediate bronchus, three occluding granulomas (one tracheal and two bronchial) as well as one case of a foreign body in the right intermediate bronchus. Two infants with right upper lobe atelectasis had a tracheal bronchus: one of them was examined soon after repair of an oesophageal atresia and had associated tracheomalacia; the second, a 1100 g premature infant, had a right lower lobe emphysema, and inflammatory stenosis of the right intermediate bronchus. The diagnostic yield of ultrathin flexible bronchoscopy was higher in cases of radiologically documented atelectasis or emphysema (80%) than in cases where these findings were absent (5/10; 50%).

The procedure was well tolerated and completed in less than two minutes. The decrease of $\mathrm{Sao_2}$ was moderate ($\mathrm{Sao_2}$ remained >80%), and resolved rapidly after removal of the fibrescope. No bradycardia was observed. None of the spontaneously breathing infants showed desaturation or bradycardia during the procedure.

In 54% of the procedures, the result of flexible bronchoscopy had a direct effect on further management: earlier correction of cardiovascular abnormalities (n=5), extraction of the foreign body (n=1), removal of a mucous plug by rigid bronchoscopy (n=1), extreme care in suctioning (no suction below the end of the endotracheal tube), a course of steroids treatment in cases of inflammatory stenosis or granulation tissue (n=6), change in ventilator settings in mechanically ventilated infants and in chest physiotherapy in spontaneously ventilated infants with severe tracheobronchomalacia (n=7).

Discussion

Our results confirm the safety and the diagnostic value of ultrathin flexible bronchoscopy in the assessment of airways in newborn and premature infants.

Evidence of persistent, clinical or radiological, airway obstruction is a constant concern in the NICU and the need for rapid evaluation of the airways constitutes a major indication for flexible bronchoscopy. However, until recently the procedure required extubation because of either the size of the paediatric bronchoscope[12] or the need for rigid bronchoscopy,[13] thereby greatly limiting the use of such exploration. With the new ultrathin flexible bronchoscope, extubation is no longer necessary for airway exploration. Previous studies demonstrated the usefulness of this procedure, but the study groups consisted of older[14] and/or nonintubated children,[8] without concomitant pathology. Other studies involved the use of either bigger bronchoscopes[5 8] or an instrument with a non-directed tip,[5 6 9 14] and the procedures were usually performed in order to verify the position of the endotracheal tube. In contrast, 80% of our patients had concomitant pathology favouring the occurrence of airway obstruction.

The addition of a connector allows the introduction of the 2·2 mm bronchoscope into the endotracheal tube, maintaining good oxygenation and ventilation, in order to achieve a more comfortable and complete examination. Our results correspond with those of Schellhase *et al*, who used the same technique and showed that after preoxygenation the procedure was well tolerated, with no serious adverse cardiovascular effects.[10] Transient hypoxaemia (Sa_{O_2} >82%) and bradycardia occurred during bronchoscopy and resolved spontaneously in less than 1 min. Ultrathin fibroscopy is well tolerated provided certain precautions are taken: it must be done in an intensive care unit, by an experienced paediatric bronchoscopist, rapidly and under cardiac and oxymetric monitoring. The absence of an operator channel prevents the suctioning of secretions, and the administration of anaesthesia or normal saline. However, careful suctioning before bronchoscopy adequately prepares the airways for the procedure. Bronchial hypersecretion precluded airway examination in only one case in our series.

Our results proved the utility of the ultrathin flexible bronchoscopy in both mechanically ventilated and spontaneously ventilating infants. When searching for airway obstruction in the presence of persistent radiological abnormalities in mechanically ventilated infants (particularly in cases of bronchopulmonary dysplasia and cardiothoracic malformations), we found that in 80% of the cases the ultrathin bronchoscope showed either endoluminal abnormalities (granuloma, inflammatory stenosis), malformation (tracheal bronchus), severe extrinsic compression, or severe tracheomalacia and/or bronchomalacia. These airway anomalies can exist concurrently and their correct diagnosis is of paramount importance in influencing management decisions and providing information for possible surgical intervention. The change in the management in 54% of our cases is a strong argument for its use. The findings of significant airway compression by a large vessel may hasten a surgical decision in infants with congenital cardiopathies. In the presence of inflammatory lesions, granuloma or tracheobronchial stenosis, due to prolonged ventilation and repeated suctioning, the suction catheter should not be passed beyond the end of the endotracheal tube, and a course of oral steroids may be given. Lastly, diagnosis of severe tracheobronchomalacia in a mechanically ventilated infant may require positive end expiratory pressure.[2] Persistent radiological abnormalities are a clear but not the sole indication for ultrathin flexible bronchoscopy. The sudden unexplained deterioration of respiratory status provides a setting in which the fibrescope offers valuable information for proper patient management.[6] Malacia and granuloma without radiological changes were particularly common in our series.

Classical paediatric flexible bronchoscopy in spontaneously ventilating infants carries the risk of inducing respiratory failure especially in small patients (≤2500 g) or in those with borderline respiratory status. Ultrathin bronchoscopy offers a safe alternative in the above mentioned circumstances.

In conclusion, the 2·2 mm ultrathin flexible bronchoscope is very useful in a NICU in improving airway exploration and the understanding of respiratory disorders during the first months of life, particularly in ventilated infants.

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Iron status, energy intake, and nutritional status of healthy young Asian children

M B Duggan, G Steel, G Elwys, L Harbottle, C Noble

Abstract

The iron status, dietary intake, and protein energy nutritional status of healthy Asian children ranging in age from 4 to 40 months was investigated. The serum ferritin, erythrocyte zinc protoporphyrin, haemoglobin and mean corpuscular haemoglobin concentrations, and mean corpuscular volume were determined in a community study of 138 children. Protein energy nutritional status was estimated by anthropometry and a four or five day weighed dietary inventory was completed by 97 children. Concentrations of the serum ferritin, haemoglobin, and mean corpuscular haemoglobin, and the mean corpuscular volume decreased progressively with increasing age. The mean values for these four indices were significantly lower in toddlers between 21 and 23 months age than in infants <6 months old. The mean erythrocyte zinc protoporphyrin was high in the first six months, later falling and rising again to peak in the 21 to 23 month age group. Thirty five per cent of children were iron deficient (serum ferritin concentration <10 µg/l) and low values for the mean corpuscular volume and mean corpuscular haemoglobin were observed in 33% and 35% respectively and 17% were anaemic (haemoglobin concentration <110 g/l). No association was observed between biochemical iron status and the dietary intake of energy or iron. Nor was there an association between protein energy nutritional status and iron status. Screening for iron deficiency in communities at risk is recommended and nutrition education using trained link workers is preferred to prophylactic iron treatment.

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In addition to its vital role as an oxygen carrier in haemoglobin and myoglobin, iron is an important cofactor in the synthesis of DNA and neurotransmitters and in mitochondrial cytochromes in many organs. Work capacity and intellectual performance in adults[1] and neurological development in young children[2 3] are adversely affected by iron deficiency. Effective treatment of iron deficiency in young children is followed by a spurt in growth and neurological development.[4]

Iron deficiency is common in children of Asian parentage.[5 6] The iron status of 138 apparently healthy Asian babies born in Sheffield was investigated during a comprehensive community nutrition study.

Subjects and methods

The overall objective was to study the relationship between diet and the nutritional and iron status of Asian children during weaning. Healthy children between 4 and 24 months of age were recruited over a 12 month period from the registers of the nine child health and general practitioner clinics which serve the majority of the Asian community. The upper age limit was later extended to 40 months in order to map the upper limit of iron deficiency. The protocol was explained in the appropriate vernacular at a home visit and informed parental consent was obtained in all cases. Recruitment and dietary and anthropometric observations were carried out under supervision (MBD and LH) by three specifically trained Asian link workers. One hundred and thirty eight parents agreed to a venous blood sample being taken from their child (MBD), and 97 of these children completed a weighed dietary inventory.

Haematological investigations included measurement of serum ferritin concentration (by immunoradiometry), erythrocyte zinc protoporphyrin (by the Protofluor Z System, Helena Laboratories) haemoglobin, red cell indices, total and differential white blood count. Iron deficiency was defined by a serum ferritin concentration <10 µg/l or a erythrocyte zinc protoporphyrin >80 µmol/mol haem. Values for the erythrocyte zinc protoporphyrin >200 µmol/mol haem (the upper limit for technical accuracy of the apparatus) were represented by 200 in statistical analysis. Haemoglobin electrophoresis was carried out when indicated by anaemia (haemoglobin <110 g/l) or abnormal red cell indices. Differences between the numbers of observations of serum ferritin (n=128) and erythrocyte zinc protoporphyrin and red cell indices (n=135 each) are due to problems with volume and clotting respectively. Children were weighed naked and crown-heel length was measured (using the Weylux Supreme beam balance and Holtain infant measuring table). Protein energy nutritional status was estimated by anthropometry, malnutrition being defined as a negative deviation in weight for body length of at least 2 SDs from the reference mean (data of the World Health Organisation (WHO) 1983).[7] A weighed dietary inventory was collected for four days (five days for children >12 months) using the PETRA electronic recording balance (Cherlyn Electronics Ltd) which obviated the need for (parental) written records. The taped nutritional information was translated from the vernacular, coded for food composition, and analysed using the Microdiet programme (Salford University) with an extended data base. The dietetic methodology will be described elsewhere in detail (M B Duggan and L Harbottle, unpublished data). Parents and general practitioners were made aware of all iron deficient children, and in most cases treatment was instituted. The study protocol was accepted by the Northern General Hospital medical ethics committee.

Results

The haematological results, grouped by age with sexes combined, are illustrated in table 1. The mean concentrations of the serum ferritin, haemoglobin, and mean cell haemoglobin, and mean cell volume (table 1) fell progressively with age to reach a nadir in the 21 to <24 months age group. The mean concentration of the erythrocyte zinc protoporphyrin, which was marginally higher in infants <6 months, rose to peak in the second year of life. The prevalence of iron deficiency estimated by the different indices is illustrated in table 2. Haemoglobinopathy was diagnosed in three children: one with β thalassaemia trait, one haemoglobin E trait, and one with combined traits for β thalassaemia and haemoglobin E. All anaemic children were iron deficient.

The daily food intakes of energy and iron were analysed according to biochemical iron status in the 97 children with available dietary data (table 3). The mean standardised energy intake and the mean iron intake was, at all ages, similar in children with low and normal serum ferritin concentrations; analyses were by Student's *t* test. The mean iron intake in both groups and at almost all ages, failed to supply the recommended daily amount for iron (5·0 mg/day, Department of Health and Social Security, 1974). The protein energy nutritional status (estimated by the weight for length SD score) is illustrated in table 3. No significant association between protein energy nutritional status and biochemical iron status was observed. The mean (SE) weight for length SD score in 45 children with low and 83 with normal serum ferritin concentrations is given by −0·559

Table 1 Haematological data on 138 healthy Asian children aged from 4 to 40 months

Age group (months)	*Ferritin (μg/l)*	*Erythrocyte zinc protoporphyrin (μmol/mol haem)*	*Haemoglobin (g/l)*	*Mean corpuscular volume (fl)*	*Mean corpuscular haemoglobin (pg)*
3–<6					
Mean	69·5	91	118·8	77·3	25·7
SE	24·02	15·42	3·26	2·12	0·64
No	8	8	8	8	8
6–<9					
Mean	37·27	77·94	114·9	72·9	24·1
SE	7·155	7·55	2·12	2·03	0·69
No	15	18	17	17	17
9–<12					
Mean	24·06	74·3	114·8	72·9	23·7
SE	3·53	4·885	1·6	1·28	0·34
No	16	20	20	20	20
12–<15					
Mean	17·07	89·69	110·9	70·6	22·9
SE	3·43	12·32	2·63	2·26	0·75
No	15	13	14	14	14
15–<18					
Mean	13·88	92·55	112·6	70·5	22·3
SE	3·033	12·1	3·58	2·31	0·71
No	17	17	17	16	16
18–<21					
Mean	19·93	90·87	109·9	69·7	22·3
SE	5·447	12·76	2·8	1·78	0·68
No	14	15	15	15	15
21–<24					
Mean	10·57*	104·8	106·8*	67·7*	21·9*
SE	2·431	16·09	4·25	3·3	1·26
No	14	13	13	13	13
24–<30					
Mean	16·82	70·68	115·2	72·1	23·9
SE	2·933	9·569	2·71	1·75	0·77
No	17	18	18	18	18
≥30					
Mean	16	89·08	108·8	68·5	22·2
SE	4·414	15·97	3·64	3·46	1·33
No	12	13	13	13	13

*Mean value for serum ferritin, haemoglobin, mean corpuscular volume, and mean corpuscular haemoglobin was significantly ($p<0·05$) lower at 21–<24 months than at 3–<6 months.

Table 2 Percentage of observations indicating iron deficiency (anaemia) in 138 healthy Asian children (the selected cut off point is in parentheses under indicator of anaemia)

Age group (months)	*Total No*	*% Ferritin deficient (<10μg/l)*	*Total No*	*% Erythrocyte zinc protoporphyrin deficient (>80 μmol/mol haem)*	*% Anaemic (haemoglobin <110 g/l)**	*% Low mean corpuscular volume (<70 fl)**	*% Low mean corpuscular haemoglobin (<23 pg)**
<12	39	10	46	35	99	18	20
12–<24	60	48	58	50	24	42	46
≥24	29	34	31	32	14	35	35
Total	128†	34	135†	41	17	33	35

*Total numbers in each group the same as for erythrocyte protoporphyrin.
†Discordance in numbers caused by insufficient volume or clotting of sample.

Table 3 Comparison of dietary energy and iron intakes and of protein energy nutritional status (weight for length SD score) according to biochemical iron status in 97 healthy Asian children, 33 with low and 64 with normal serum ferritin concentration

Age group (months)	*Iron deficient (serum ferritin <10 μg/l)*			*Iron adequate (serum ferritin ≥10 μg/l)*		
	Energy intake (kJ/kg/day)	*Iron intake (mg/day)*	*Weight for length SD score*	*Energy intake (kJ/kg/day)*	*Iron intake (mg/day)*	*Weight for length SD score*
<6						
Mean	No values	No values	No values	349	5·72	−0·28
SE				37	0·48	0·285
No				13	13	13
6–<12						
Mean	345	3.17	0·11	316	4·15	−0·27
SE	32	0.39	0·462	23	0·54	0·232
No	6	6	6	19	19	19
12–<18						
Mean	353	4.91	−0·42	354	3·72	−1·0
SE	39	0.91	0·266	32	2·10	0·192
No	14	14	14	13	13	13
18–<24						
Mean	264	2.56	−1·28	337	4·81	−0·21
SE	30	0.41	0·299	32	1·17	0·417
No	7	7	7	9	9	9
≥24						
Mean	302	3.81	0·56	322	3·34	−0·9
SE	31	0.75	0·62	38	0·55	0·292
No	6	6	6	10	10	10

(0·1149) and −0·3844 (0·1417) respectively (analysed by Student's *t* test; this was not significant).

Discussion

How well do our data represent the situation in Sheffield? We located the parents of 310 of the estimated 600 eligible chidren aged 4 to 24 months and registered in the selected geographical area. Agreement to take part and completion of the dietary study appeared to reflect maternal confidence and control of decision making and the vulnerable may have been under represented. The 29 children >24 months may be less representative of their age group.

Our observation of a high prevalence of iron deficiency in Asian toddlers agrees with reports from other British cities.[5 6 8 9] Our results delineate the gradual deterioration with increasing age of a number of haematological indicators of iron status. We attempted to identify risk factors for iron deficiency and failed to demonstrate any association between present iron deficiency and previous low birth weight, initial feeding method, or age at commencement of weaning. Birthweight data were available on 113 children (mean 3100 g). Fourteen (17%) had been of low birth weight, and four (28%) of these were iron deficient compared with 32% of children born at a normal birth weight (not significant by χ^2). Twenty four (17%) of the 140 children with information on initial feeding method had been exclusively breast fed for four months and 80% had started solids by 6 months of age. Inspection of the data suggested no effect on iron status attributable to differences in infant feeding method, or to the age of starting weaning. Intestinal blood loss due to parasites was not investigated. It is manifestly not a problem in this city and can probably be discounted.

Our data suggest that iron status is lowest more than a year after the commencement of weaning. How satisfactory was the weaning diet? Although the mean energy intake at all ages, and irrespective of iron status, was lower than the WHO (1985) recommendations,[9] it was reasonably close to recorded intakes by healthy English children.[10] The fat and protein energy composition was acceptable (unpublished data, M B Duggan and L Harbottle). Their satisfactory protein energy nutritional status (table 3) is supportive evidence for the adequacy of the children's dietary intake. The similar levels of energy intake in iron deficient and iron adequate children suggest that iron deficiency had no significant effect on appetite (intake). Warrington and Storey compared a group of healthy Asian children with white controls matched for age and socioeconomic status.[10 11] They observed a higher prevalence of iron deficiency in Asian children despite similar rates of both growth and similar dietary intakes of energy and iron. In this study the mean dietary iron intake in all children failed, at most ages, to meet the recommended daily amount for iron.

The surprising observation of a similarly low level of iron intake in biochemically iron deficient and non-deficient children needs to be considered in context. Firstly, the estimate of iron intake given by food composition tables is approximate, and it does not distinguish between haem and non-heam iron. Furthermore iron intake is expressed in mg/day without reference to body weight or energy intake, although no difference between the two groups emerged from analysis of data expressed in mg iron/418 kJ (100 kcal). In the absence of an ideal biomarker for iron deficiency, serum ferritin concentration was selected as an indicator. The serum ferritin has a skewed distribution, and although the concentration falls at an early stage of deficiency, the cut off point for a diagnosis of iron deficiency is somewhat arbitrary. A low concentration may rise during infection giving a false negative result. Any of these factors may have blurred distinctions between truly deficient and normal children. Nevertheless, the significant linear correlation between serum ferritin (y) and iron intake (x) (r=0·22; *t*=2·20 with 95 df) suggests that iron status is influenced by iron intake. Erythrocyte zinc protoporphyrin is also an imperfect indicator. The concentration of erythrocyte zinc protoporphyrin is physiologically high soon after birth and discordance between the erythrocyte zinc protoporphyrin and the other indicators in children <12 months is evident in table 2.

Subtle dietary differences over long periods of time, and imperfectly estimated in a cross sectional study, cannot be appreciated or quantified in a few days' observations. A longitudinal study would permit analysis of the long term effects of differences in the progress and practice of weaning. It might also help to explain the observation of adequate iron status in children who may have had low iron intakes since birth. The possible effects of vitamin C on the bioavailability of non-haem iron, or of riboflavin on iron turnover were considered. Inspection of data failed to demonstrate a link between intake of vitamin C or riboflavin and the concentration of serum ferritin. Nor was the trend towards a higher prevalence of iron deficiency in fresh milk fed children significant.[10] Reliance on sweet foods by parents attempting to maintain a Halal* diet and to follow the local weaning mores is well recognised.[12–14] Ignoring the considerable contribution of cows' milk to commercial baby foods, fresh or formula milk was the major energy source (providing more than 60% of dietary energy) until the age of 18 months. Milk is a poor source of iron and the bioavailability of iron in both formula and cows' milk is uncertain.

In socioeconomically deprived areas with a high proportion of Asian children, late weaning on to iron poor diets may result in a greater problem than is apparent in Sheffield.[12 13] These and previous findings suggest that more than a third of British Asian babies may be iron deficient.[5–7] In the absence of a link between protein energy nutrition and biochemical iron status, they may not be identified as at risk. We strongly support the case for screening for iron deficiency in vulnerable groups, which was cautiously proposed by the joint working party on child health surveillance.[14] We would favour the use of a more sensitive indicator than the haemoglobin concentration (M B Duggan, *et al*, unpublished observations).

Prevention of iron deficiency is the next consideration. In view of the fact that iron supplementation of formula did not protect against iron deficiency, should we recommend iron prophylaxis as for other 'at risk' babies such as the previously low birth weight? If so, when should they be treated? Our link workers reported complaints and confusion over iron dosages dispensed for our iron deficient children. We predict that general prophylaxis would prove neither feasible nor acceptable. The link with socioeconomic deprivation reported from rich[15] and poor countries[1] suggests that preventive nutrition education may be a preferable option. Appropriately trained and supported link workers would give practical nutrition teaching based on weaning recipes developed by (Asian) nutritionists, to all Asian mothers attending child health clinics.[16]

Although poverty, linguistic isolation, and difficulties in adaptation of Halal diets for weanlings have combined to make this a particularly vulnerable group, iron deficiency is not confined to Asian children.[5 8] If the reported association between relatively mild, that is, non-anaemic iron deficiency and delay in neurological development is confirmed, the present findings will have broader implications for child health.

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*Most Sheffield Asians follow the Koranic injunction to avoid pork and to eat only Halal meat which has been ritually slaughtered and dedicated to Allah.

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Diet and faecal flora in the newborn: iron

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Abstract

The faecal flora of a baby receiving a modern infant formula is substantially different from that of a breast fed baby. This difference is a little less when whey based formulas are used. The addition of bovine lactoferrin has no effect and there is some evidence that the presence of added iron in a formula moved the faecal flora further away from that of a breast fed baby.

The iron content of currently used infant formulas is much higher than that of breast milk. The effect of the addition of iron to both whey and casein based formulas on the faecal flora was examined in further detail. Faecal flora were examined at 14 days of age in 33 babies receiving a whey formula fortified with iron, 29 babies receiving a whey formula without iron, 29 babies receiving a casein formula fortified with iron, and 24 babies receiving casein formula without iron. Subsequently fewer babies in each group were examined at week 7, 11, and 15. The addition of iron to both casein and whey formulas discouraged colonisation and growth of staphylococci and bacteroides but encouraged the colonisation and growth of clostridia and enterococci. The type of protein and not the iron content had more effect upon the growth of bifidobacteria; both whey formulas, fortified or not, encouraged the colonisation by bifidobacteria. If an infant formula, for use in the first few months, is to mimic the physiological effects of breast milk, there may be microbiological arguments for not fortifying it with iron. However, large empirical trials would be necessary before advocating such a policy.

In previous studies in this series we have shown that (1) despite extensive modification of cows' milk when manufacturing an infant formula to render its composition closer to that of human milk the faecal flora of the bottle fed baby remained substantially different from that of the breast fed baby, in particular an increased colonisation by bifidobacteria in breast fed babies.[1] (2) Whey based formulas, rather than casein predominant ones, result in a faecal flora a little closer to the breast fed baby.[2] (3) The addition of *bovine* lactoferrin to an infant formula did not move the faecal flora in the direction of breast milk and there was some evidence that the presence of added iron in a formula moved the faecal flora away from a breast milk flora.[3]

The iron content of breast milk is very low (0·7–1·5 mg/l) yet the breast fed infant is able to absorb that iron very efficiently. Iron is not absorbed as well from an infant formula derived from cows' milk, although adapted to mimic breast milk as much as possible.[4] The reduced bioavailability of iron from infant formulas has encouraged the addition of iron to a formula (5·0–7·0 mg/l) at a much higher level than in breast milk. All of the infant formulas available in Britain and most of those available world wide are fortified with iron.

This study examines the effect of the removal of iron from both casein and whey predominant formulas upon the faecal flora of infants at 14 days and at 7, 11, and 15 weeks of age.

Subjects and methods

DIET AND BABIES

Mothers from one postnatal ward who had delivered vaginally a baby at term weighing more than 2500 g and who had definitely decided to bottle feed were invited to take part in the study. If they agreed and gave written consent their babies were allocated to receive either a predominantly casein or whey formula neither of which contained added iron. The study was carried out over a 10 month period from January to October 1989. The type of formula allocated to each new baby recruited to the study changed at the beginning of each month. Babies recruited in the first month were allocated the casein formula and those recruited the next month were allocated the whey formula and so on. Once allocated to a particular formula a baby continued to receive that one throughout the 15 weeks that it took part in the study. A number dropped out or were withdrawn before the full 15 weeks were completed, mostly because of the introduction of weaning foods. The results of babies in this study are compared with those obtained from babies who had been delivered in the same delivery suite and cared for on the same postnatal ward but who were fed normal iron fortified whey or casein predominant formula.[2] Details of the four groups are shown in table 1. The use of historical controls is not ideal but there are problems of logistics and expense in repeating the same study.

The composition of the formulas used in this and the previous study are shown in table 2. The whey predominant formulas were Gold Cap SMA (Wyeth) with added iron or without iron and the casein predominant formulas were White Cap SMA (Wyeth) again with added iron or without iron. The iron content of the non-fortified formulas was similar to that of breast

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milk. The non-fortified formulas were supplied as 'ready to feed' liquid milk throughout the study. The fortified formulas had been supplied as 'ready to feed' for the first 3 weeks when they changed to feeds prepared from powder. From the end of the study (age 15 weeks) all babies received a 'normal' iron fortified formula.

PROCEDURES

Faeces were collected at week 2, 7, 11, and 15. Anthropometry was recorded on day 1. A heelprick specimen of blood was taken at week 7, 11, and 15 for measurement of haemoglobin, mean cell volume, and mean cell haemoglobin. The methods for microbiological examination of faeces were exactly as described in the previous studies in this series.[1]

STATISTICAL ANALYSIS

The results were analysed statistically using Mann-Whitney, Wilcoxon, χ^2, and Student's *t* test as appropriate.

ETHICAL APPROVAL

Approval for the study was obtained from the ethics committee of the South Birmingham Health Authority. The mothers of all babies taking part in the study gave written informed consent.

Table 1 Data of babies taking part in the study

	Formula			
	Whey with iron	*Whey without iron*	*Casein with iron*	*Casein without iron*
Day 14				
No of babies	33	29	29	24
Sex				
Male	15	20	12	7
Female	18	9	17	17
Race				
White	32	29	26	21
Asian	0	0	1	2
Afro-Caribbean	1	0	2	1
Mean (SD) birth weight (g)	3520 (490)	3290 (520)	3340 (380)	3270 (300)
No of babies				
Week 7	17	22	16	22
Week 11	10	22	13	18
Week 15	9	20	13	13

Table 2 Composition of the fortified and non-fortified formulas compared with breast milk (per litre)

	Breast milk	*Formula*			
		Whey with iron	*Whey without iron*	*Casein with iron*	*Casein without iron*
Protein (g) (nitrogen×6·36)	11	15	15	15	15
Total 'true' protein (g) (%)	9 (100)	13 (100)	13 (100)	14 (100)	14 (100)
Caseins (%)	2·5 (28)	5·2 (40)	5·2 (40)	11·1 (79)	11·1 (79)
Whey proteins (%)	6·5 (72)	7·8 (60)	7·8 (60)	2·9 (21)	2·9 (21)
Phosphorus (mg)	150	330	330	450	450
Iron (mg)	0·8	6·7	0·6	6·7	0·6

Proteins for breast milk based on Hambraeus[5] and for formulas calculated from manufacturers' information and Jennes and Sloan.[6] Minerals for breast milk based on DHSS 1977.[7]

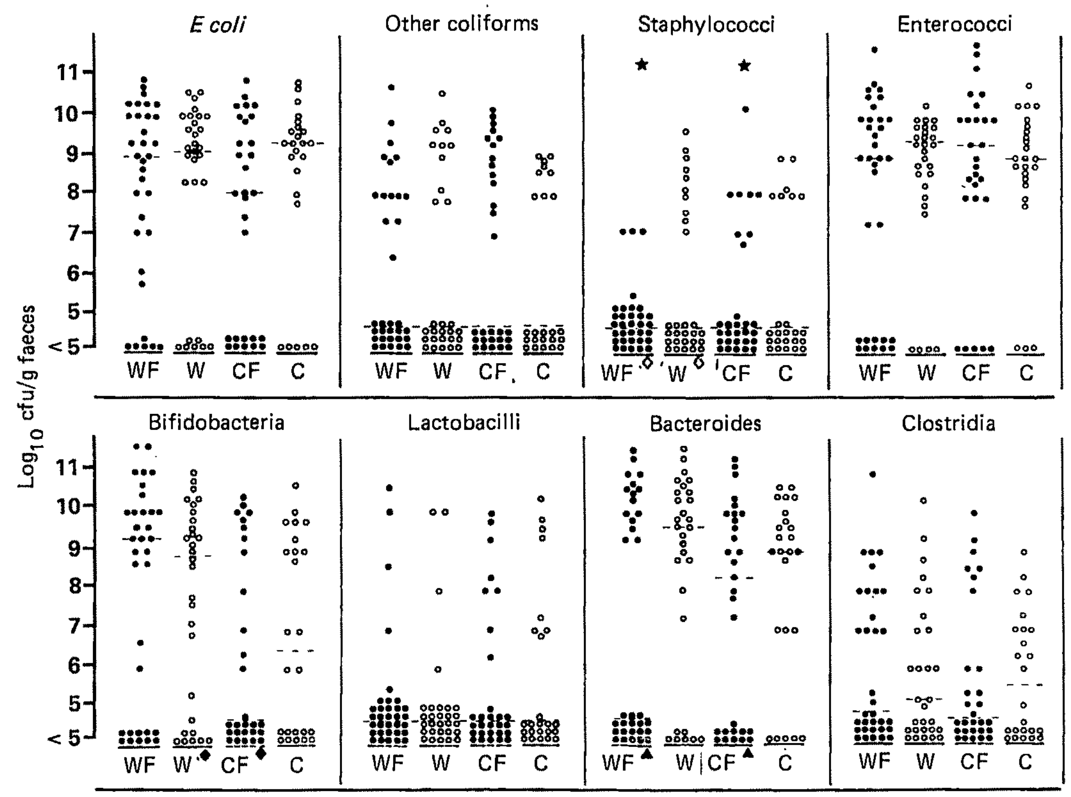

Figure 1 Counts of individual organisms ($\log_{10}$ colony forming units (cfu)/g faeces) in the four dietary groups on day 14. Median count shown by a horizontal broken line. WF, whey with iron; W, whey without iron; CF, casein with iron, C, casein without iron. (Solid circles indicate fortified and clear unfortified formulas.) ★ Distribution of counts significantly different for babies fed casein with iron and whey with iron compared with casein without iron and whey without iron, $p=0·04$. ◇ Proportion of babies colonised significantly different for babies fed whey with iron compared with babies fed whey without iron, $p=0·02$. ◆ Proportion of babies colonised significantly different for babies fed casein with iron compared with babies fed whey without iron, $p<0·05$. ▲ Proportion of babies colonised significantly different for babies fed whey with iron and casein with iron compared with casein without iron and whey without iron, $p<0·02$.

Table 3 Comparison of faecal flora at week 7 (counts expressed as ×10⁹/g)

	Formula			
	Whey with iron (n=17)	*Whey without iron (n=22)*	*Casein with iron (n=16)*	*Casein without iron (n=22)*
E coli				
No (%) of babies colonised	15 (88)	16 (73)	11 (69)	20 (91)
Median count	0·5	0·96	0·04	1·85
Range of counts	0–20	0–50	0–600	0–63
Other coliforms				
No (%) of babies colonised	2 (12)	8 (36)	6 (38)	6 (27)
Median count	0	0	0	0
Range of counts	0–8	0–7·30	0–10	0–1·30
Bifidobacteria				
No (%) of babies colonised	13 (76)	19 (86)	10 (63)	14 (64)
Median count	2	1·45	0·1	0·01
Range of counts	0–90	0–33	0–20	0–16
Lactobacilli				
No (%) of babies colonised	3 (18)	3 (14)	4 (25)	6 (27)
Median count	0	0	0	0
Range of counts	0–0·1	0–13·4	0–10	0–4·30
Staphylococci				
No (%) of babies colonised	0	4 (18)	5 (31)*	0*
Median count	0	0	0	0
Range of counts	0	0–1·30	0–3	0
Enterococci				
No (%) of babies colonised	16 (94)	20 (91)	15 (94)	22 (100)
Median count	1·0	0·65	0·3	1·80
Range of counts	0–20	0–9	0–1700	0–53
Bacteroides				
No (%) of babies colonised	12 (71)¶	19 (86)¶	7 (44)*¶	18 (82)*¶
Median count	4	3·45§	0·000005‡§	3·45‡
Range of counts	0–300	0–130	0–30	0–100
Clostridia				
No (%) of babies colonised	9 (53)	14 (64)	14 (88)*	10 (45)*
Median count	0·00001	0·001	0·01†	0†
Range of counts	0–1·0	0–23	0–0·3	0–0·26

Significant differences between babies fed a formula without iron and those with a formula fortified with iron: *using χ^2 test, $p<0\cdot05$; †using Mann-Whitney test, $p<0\cdot05$; ‡using Mann-Whitney test, $p=0\cdot008$.
Significant differences between babies fed whey without iron and casein with iron: §using Mann-Whitney test, $p<0\cdot02$.
Significant differences between babies fed both casein and whey formulas without iron and casein and whey formulas with iron: ¶using χ^2 test, $p<0\cdot02$.

Table 4 Comparison of faecal flora at week 11 (counts expressed as ×10⁹/g)

	Formula			
	Whey with iron (n=10)	*Whey without iron (n=22)*	*Casein with iron (n=13)*	*Casein without iron (n=18)*
E coli				
No (%) of babies colonised	9 (90)	18 (82)	11 (85)	15 (83)
Median count	1·05	0·51	2	1·10
Range of counts	0–30	0–4	0–20	0–16
Other coliforms				
No (%) of babies colonised	4 (40)	13 (59)	6 (46)	8 (44)
Median count	0	0·06	0	0
Range of counts	0–1	0–2	0–10	0–10
Bifidobacteria				
No (%) of babies colonised	9 (90)	18 (82)	9 (69)	11 (61)
Median count	1·0	0·70	1·0	0·06
Range of counts	0–30	0–62	0–20	0–17
Lactobacilli				
No (%) of babies colonised	2 (20)	2 (9)	2 (15)	5 (28)
Median count	0	0	0	0
Range of counts	0–0·4	0–0·02	0–0·3	0–26
Staphylococci				
No (%) of babies colonised	2 (20)	3 (14)	2 (15)	5 (28)
Median count	0	0	0	0
Range of counts	0–5	0–0·20	0–1	0–0·1
Enterococci				
No (%) of babies colonised	9 (90)	20 (91)	11 (85)	16 (89)
Median count	0·15	0·25	1·0	0·38
Range of counts	0–20	0–7·60	0–20	0–30
Bacteroides				
No (%) of babies colonised	7 (70)	19 (86)‡	5 (38)*‡	15 (83)*
Median count	0·22†	5·30†	0	3·30
Range of counts	0–20	0–53	0–30	0–21·30
Clostridia				
No (%) of babies colonised	7 (70)	8 (36)	8 (62)	9 (50)
Median count	0·00055†	0†§	0·01§	0·000005
Range of counts	0–1	0–2·0	0–0·1	0–1

Significant differences between babies fed a formula without iron and those fed a formula fortified with iron: *using χ^2 test, $p<0\cdot05$; †using Mann-Whitney test, $p<0\cdot05$.
Significant differences between babies fed whey without iron and casein with iron: ‡using χ^2 test, $p<0\cdot05$; §using Mann-Whitney test, $p<0\cdot05$.

Results

The results are shown in two ways: (1) counts of individual *organisms* examined in each baby, analysed statistically using the Mann-Whitney test, and the presence or absence of an organism analysed by the χ^2 test (fig 1 for day 14, tables 3–5 for weeks 7, 11, and 15). (2) Patterns of dominance in individual *babies* (that is a particular genus accounting for the highest count in the bacterial population examined); these were analysed statistically by the χ^2 test (fig 2 for day 14 and week 15).

(1) COUNTS OF INDIVIDUAL ORGANISMS

Whey formulas: with or without added iron

The presence of added iron was associated with the following:

(a) Fewer babies colonised with staphylococci at day 14 (3 (12%) compared with 10 (35%), $p=0\cdot02$, fig 1).

(b) Fewer babies colonised with *Escherichia coli* at 15 weeks (44% compared with 90%, $p<0\cdot05$, table 5).

(c) Fewer babies colonised with bacteroides at day 14 (15 (48%) compared with 22 (76%), $p=0\cdot06$, fig 1) and at 15 weeks (33% compared with 95%, $p<0\cdot01$, table 5).

(d) Babies had lower counts of bacteroides in their faeces at week 15 ($p<0\cdot01$, table 5).

(e) Babies had higher counts of clostridia at week 15 ($p<0\cdot01$, table 5).

Casein formulas: with or without added iron

The presence of added iron was associated with:

(a) More babies colonised with staphylococci at 7 weeks (31% compared with 0, $p<0\cdot05$, table 3).

(b) Fewer babies colonised with bacteroides at 11 weeks (38% compared with 83%, $p<0\cdot05$, table 4).

(c) More babies colonised with clostridia at 7 weeks (88% compared with 45%, $p<0\cdot05$, table 3).

(d) Babies had higher counts of clostridia at 7 weeks ($p<0\cdot05$, table 3).

Casein and whey formulas: with or without added iron

The presence of added iron was associated with:

(a) Fewer babies colonised with bifidobacteria at day 14 (44% fed casein with iron compared with 76% fed whey without iron, $p<0\cdot05$, fig 1).

(b) Babies had lower counts of staphylococci at day 14 (casein with iron and whey with iron compared with casein without iron and whey without iron) ($p=0\cdot04$, fig 1).

(c) Fewer babies colonised with bacteroides at day 14 (55% fed casein with iron and whey with iron compared with 77% fed casein without iron and whey without iron, $p<0\cdot02$, fig 1), at 7 weeks (58% fed casein with iron and whey with iron compared with 84% fed casein without iron and whey without iron, $p<0\cdot02$, table 3), and at 11 weeks (38% fed casein with iron compared with 83% fed casein without iron and 86% fed whey without iron, $p<0\cdot05$, table 4).

Table 5 Comparison of faecal flora at week 15 (counts expressed as $\times 10^9$/g)

	Formula			
	Whey with iron (n=9)	*Whey without iron (n=20)*	*Casein with iron (n=13)*	*Casein without iron (n=13)*
E coli				
No (%) of babies colonised	4 (44)*	18 (90)*	13 (100)	12 (92)
Median count	0	0·24	1	1·60
Range of counts	0–40	0–4·6	0–30	0–13
Other coliforms				
No (%) of babies colonised	5 (56)	7 (35)	2 (11)	7 (54)
Median count	0·0001	0	0	0·01
Range of counts	0–10	0–7·6	0–0·1	0–4·60
Bifidobacteria				
No (%) of babies colonised	5 (56)	13 (65)	8 (62)	10 (77)
Median count	0·004	0·23	0·9	0·03
Range of counts	0–10	0–36	0–20	0–43
Lactobacilli				
No (%) of babies colonised	1 (11)	3 (15)	3 (23)	2 (15)
Median count	0	0	0	0
Range of counts	0–0·4	0–1·10	0–1	0–16
Staphylococci				
No (%) of babies colonised	2 (22)	2 (10)	3 (23)	1 (8)
Median count	0	0	0	0
Range of counts	0–0·02	0–0·03	0–0·2	0–0·06
Enterococci				
No (%) of babies colonised	8 (89)	18 (90)	13 (100)	12 (92)
Median count	1	0·37‡	2‡	0·60
Range of counts	0–10	0–3·0	0–10	0–40
Bacteroides				
No (%) of babies colonised	3 (33)†	19 (95)†	9 (69)	12 (92)
Median count	0‡	4·45‡§	0·2§	2·60
Range of counts	0–20	0–70	0–20	0–26
Clostridia				
No (%) of babies colonised	5 (55)	6 (30)	10 (77)	9 (69)
Median count	0·00001‡	0‡	0·01	0·0001
Range of counts	0–20	0–0·01	0–0·5	0–0·60

Significant differences between babies fed a formula without iron and those with a formula fortified with iron: *using χ^2 test, $p<0{\cdot}05$; †using χ^2 test, $p<0{\cdot}01$; ‡using Mann-Whitney test, $p<0{\cdot}01$. Significant differences between babies fed whey without iron and casein with iron: §using Mann-Whitney test, $p<0{\cdot}01$.

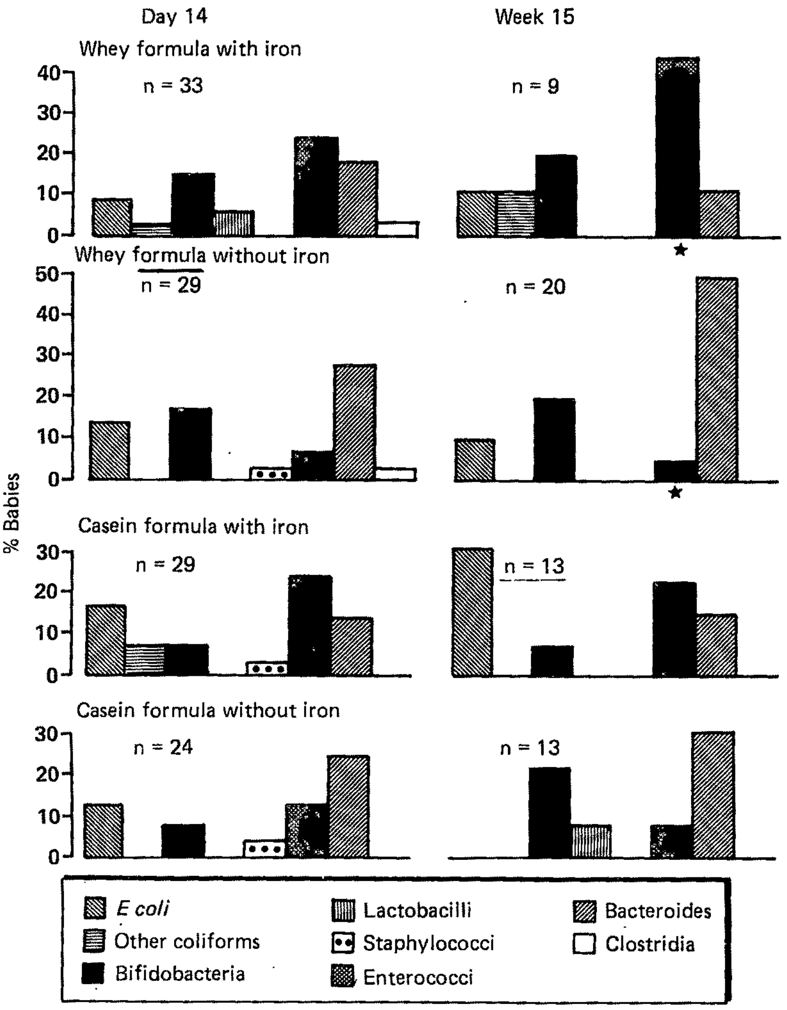

Figure 2 Percentage of babies in whose faeces organisms were dominant at day 14 and week 15; ★ Number of babies significantly different ($p<0{\cdot}05$) from babies fed an iron fortified formula.

(d) Babies had higher counts of bacteroides at 7 weeks (whey without iron compared with casein with iron, $p=0{\cdot}02$, table 3).

Differences between casein and whey formulas

A whey formula was associated with:

(a) More babies colonised with bifidobacteria at day 14 (73% fed whey formulas compared with 51% fed casein formulas, $p<0{\cdot}05$, fig 1).

(b) Higher counts of bifidobacteria at day 14 ($p=0{\cdot}003$, fig 1).

(c) Fewer babies colonised with clostridia at 15 weeks (38% compared with 73%, $p<0{\cdot}05$, table 5).

Changes with time

The effect of time upon the faecal flora in each baby was analysed using the Wilcoxon test. No changes were found in any of the babies fed either of the casein formulas or the whey with iron formula.

More babies fed whey without iron acquired *E coli* throughout the study: but the counts fell from day 14 to week 15 ($p=0{\cdot}018$). The counts of enterococci in these babies fell ($p=0{\cdot}021$) throughout the same period and fewer babies fed whey without iron had clostridia in their faeces at the end of the study ($p=0{\cdot}007$).

(2) PATTERNS OF DOMINANCE

There was no significant difference in the patterns of dominance in the faeces at day 14 (fig 2). At week 15 more babies on whey with iron (44%) had a dominance of enterococci than babies on whey without iron (5%) ($p<0{\cdot}05$).

(3) HAEMATOLOGY

Table 6 shows the concentrations of haemoglobin, mean cell volume, and mean cell haemoglobin. Iron fortification was associated with a rise in haemoglobin and a maintenance rather than a fall in mean cell haemoglobin.

Discussion

DIETARY DIFFERENCES

The different effects of a casein and whey formula and their associated different nutrients confirm our previous observations, that is, increased colonisation by bifidobacteria in babies fed a whey formula.[2] The main object of this study though was to compare the effect of iron on the composition of the faecal flora. Iron in both casein and whey formulas discouraged staphylococci and bacteroides but encouraged clostridia and enterococci, that is, the pattern of flora being generally different from that of the breast fed baby. A similar study in Holland looking at the effect of iron to a whey formula showed that the addition of iron had the same overall effect in that the flora was more dissimilar to that of the breast fed baby.[8, 9] There are some similarities in the flora of babies fed iron free formulas and breast fed babies,

Table 6 Haematological measurements of babies throughout the study

	Formula			
	Whey with iron	*Whey without iron*	*Casein with iron*	*Casein without iron*
Week 7				
Mean (SD) haemoglobin (g/l)	115 (8·0)*	105 (9·0)*	117 (8·0)	108 (15·0)
Mean (SD) cell volume (fl)	89·9 (5·8)*‡	97·2 (4·1)*	88·0 (3·3)†‡	96·3 (6·1)†
Mean (SD) cell haemoglobin (pg)	32·5 (1·1)*	31·2 (1·4)*‡	33·3 (1·4)†	30·9 (2·2)†‡
Week 11				
Mean (SD) haemoglobin (g/l)	117 (12·0)*	107 (10·0)*	119 (8·0)†	111 (12·0)†
Mean (SD) cell volume (fl)	85·6 (6·0)*	89·8 (3·3)*	83·5 (3·3)†	89·5 (4·4)†
Mean (SD) cell haemoglobin (pg)	32·2 (1·9)*	29·1 (1·3)*	33·4 (0·7)†	28·9 (1·5)†
Week 15				
Mean (SD) haemoglobin (g/l)	124 (9·0)*	103 (11·0)*	127 (4·0)†	102 (7·0)†
Mean (SD) cell volume (fl)	83·5 (7·0)‡	85·4 (4·7)	83·0 (2·1)‡	86·2 (4·0)
Mean (SD) cell haemoglobin (pg)	32·7 (1·4)*	27·3 (1·6)*‡	32·9 (1·1)†	27·2 (1·6)†‡

Significant differences between: *babies fed whey with iron compared with whey without iron at the same age using *t* test, p<0·05; †babies fed casein with iron compared with casein without iron at the same age using *t* test, p<0·05; ‡babies at 7 weeks and 15 weeks receiving the same formula using paired *t* test, p<0·001.

particularly with regard to staphylococci and clostridia. Nevertheless the faecal flora of the babies fed a formula without iron were not dominated by bifidobacteria and the faecal flora remained substantially different from that of breast fed babies.

GUT PHYSIOLOGY

Lactobacilli and bifidobacteria are among the few organisms that can survive without the presence of iron.[10] It is thought that much of the free iron in the gut of a breast fed baby is attached to lactoferrin (present in breast milk) thus rendering it unavailable for utilisation by micro-organisms.[11] This is one mechanism to explain the predominance of bifidobacteria and lactobacilli in the faeces of breast fed babies compared with formula fed babies. The converse could also explain the predominance of iron dependent organisms, for example, *E coli* in the faeces of formula fed babies. In this study, however, though the absence of iron did have microbiological effects these were *not* the promotion of lactobacilli and bifidobacteria. Indeed protein quality (casein or whey) had a clearer effect on the appearance of these organisms than did the presence or absence of iron. This illustrates the complex interaction of nutrients in a milk or formula which affect the faecal flora.

CLINICAL SIGNIFICANCE

The clinical significance of these microbiological effects of iron is unclear. Although definite, they were small, with a whey based formula without iron resulting in a faecal flora very distant from a breast fed baby. Does it matter what organisms a baby has in his bowel so long as they are not invasive? If the aim of an infant formula is to mimic not only the composition of breast milk but also its physiological effects, for example, on growth, biochemistry, faecal flora, etc, then the omission of added iron, particularly from a whey formula, gives a faecal flora closer to breast milk in that staphylococci are encouraged and clostridia and enterococci are discouraged. There may be an argument therefore to use a 'starting' formula which is not fortified with iron during the early months of life probably to be followed in later infancy by one containing iron as iron stores are depleted.

The haematology results are impossible to interpret completely as we did not have comparable values for babies receiving breast milk. However they at least raise some caution before advocating widespread use of non-iron fortified formulas especially after the first month of life. Clearly more extensive empirical trials are necessary to determine the exact use of unfortified formulas in the first few months of life.

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Intraluminal biliary obstruction

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Abstract

Jaundice caused by intraluminal bile duct obstruction in infancy is rare but may occur in association with biliary sludge, inspissated bile plugs, or gall stones. Nine boys (age 2 weeks–6 months) with obstruction caused by inspissated bile (n=7) or gall stones (n=2) are presented. Haemolysis was not a factor in the patients' histories but an abnormal entry of the common bile duct into the third part of the duodenum was demonstrated in two and one had an asymptomatic haemangioma. Ultrasonography was the most useful investigation. Surgical removal of the bile duct obstruction was necessary in eight cases and included biliary tract drainage in six and cholecystectomy for changes of cholecystitis in four. Obstruction resolved spontaneously in one infant after percutaneous cholangiography. There were no postoperative complications.

Inspissated bile plug syndrome (IBPS) as a cause of neonatal obstructive jaundice is a well recognised complication of neonatal haemolysis caused by maternal rhesus and ABO blood group incompatibility.[1] The development of early exchange transfusion reduced the incidence.[1] An increase in the number of reported cases in recent years has been attributed to parenteral nutrition, diuretic treatment,[2] bowel dysfunction,[3] and disseminated intravascular coagulation.[4] The presence of an obstruction of the common bile duct in neonates and young infants caused by inspissated bile or gall stones in the absence of any of the above factors is unusual.[5] Seven infants with obstruction caused by inspissated bile and two by gall stones are presented and the possible predisposing factors discussed.

Patients

Seven boys presented at a mean age of 6 weeks (range 2 weeks–3 months) with jaundice, pale stool, and dark urine (see table 1 for patients' details). Another two boys presented at 4 and 6 months of age with obstructive jaundice secondary to stones in the common bile duct. Three of the nine had had significant obstetric complications: these included fetal distress, forceps delivery, and maternal eclampsia treated by caesarean section at 37 weeks' gestation. The mean birth weight was 3210 g (range 2400-3800 g) and the mean gestational age was 40 weeks (range 37–42 weeks). Four children developed neonatal problems including physiological jaundice that settled spontaneously, anaemia treated by blood transfusion, hypoglycaemia where there was a family history of consanguinity, and hepatic haemangiomas diagnosed on ultrasound. The hepatic haemangiomas were asymptomatic and no specific treatment was given.

All nine patients presented with a conjugated hyperbilirubinaemia. There was a wide variation in bilirubin concentration (mean 133 μmol/l, range 56–324 μmol/l), alkaline phosphatase activity (mean 917 IU/l, range 546–1963 IU/l), and aspartate aminotransferase activity (874 IU/l, range 157–179 IU/l). The haemoglobin concentration ranged from 91–122 g/l. The reticulocyte count as a percentage ranged from 1·8–4·2% and no significant haemolysis was identified.

DISIDA (technetium labelled diisopropyliminodiacetic acid) scans were performed in five patients, of whom four showed no excretion, suggesting a diagnosis of biliary atresia. One showed minimal excretion at six hours. Liver biopsy specimens taken from four patients (table 2) showed features of cholangitis and duct obstruction in two cases, cholestasis with mild portal fibrosis in one case, and bile duct proliferation in one.

Ultrasound scan results are shown in table 2. The extrahepatic biliary tree was dilated in eight cases. One child was incorrectly thought to have a choledochal cyst as the diameter of the

Table 1 Clinical details of patients with IBPS and gall stones

Patient No	*Age*	*Symptoms*	*Neonatal history*	*Family history*
			IBPS	
1	12 weeks	Jaundice	None	None
2	6 weeks	Jaundice	Forceps delivery, special care baby unit	None
3	4 weeks	Jaundice	None	None
4	2 weeks	Jaundice	Blood transfusion	Diabetes
5	10 weeks	Jaundice	Caesarean section, eclampsia, hypoglycaemia	Consanguinous
6	2 weeks	Jaundice	Capillary haemangiomas	None
7	8 weeks	Jaundice	None	None
			Gall stones	
8	6 months	Jaundice	Jaundice	None
9	4 months	Jaundice	None	None

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Table 2 Findings on investigations performed

Patient No	*DISIDA scan*	*Liver biopsy*	*Ultrasound scan*	*Percutaneous transhepatic cholangiography*
1	No excretion	Cholangitis	Dilated common bile duct, dense bile	Free drainage, cystic duct into confluence of right and left hepatic duct
2	No excretion	—	Bile plug, ? Mirrizi's syndrome	—
3	—	—	Dilated common bile duct and gall bladder, inspissated bile	Obstructed lower common bile duct
4	No excretion	—	Dilated common bile duct (8 mm), ? choledochal cyst	—
5	? Excretion 6 hours	Cholestasis, bile duct proliferation	Normal	—
6	No excretion	—	Dilated common bile duct and gall bladder, haemangiomas	—
7	—	Cholangitis, features of duct obstruction	Dilated biliary tree	Obstructed lower common bile duct
8	—	Biliary cholestasis, mild portal fibrosis	Gall bladder stones, dilated common bile duct	Stones in cystic duct and common bile duct
9	—	—	Common bile duct stones	—

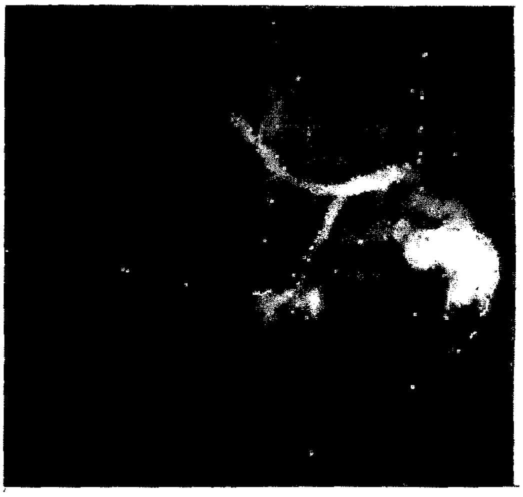
Table 3 Details of treatment and outcome

Patient No	*Operation performed*	*Findings at operation*	*Results of operctive cholangiogram*	*Procedure*	*Follow up (months)*
1	No	(spontaneous resolution)	—	—	—
2	Yes	Dilated common bile duct, chronically inflamed gall bladder	Filling defect in cystic duct	Cholecystectomy, ECBD, T-tube	6, well
3	Yes	Tense common bile duct and gall bladder, bile plug removed	Bile plug, ? papillary stenosis	Cholecystectomy, ECBD, T-tube, sphincteroplasty	1, well
4	Yes	Dilated common bile duct and gall bladder, bile plug and debris	Dilated common bile duct, common bile duct into third part duodenum	ECBD, T-tube, dilatation of ampulla	1, well
5	Yes	Inspissated bile plug	Normal	Cholecystostomy, saline flush	1, well
6	Yes	Haemangiomas, two hepatic arteries, inspissated bile	Normal	Cholecystostomy, saline flush	1, well
7	Yes	Dilated biliary tree, inspissated bile	Common bile duct into third part duodenum	Choledochoduodenostomy, ECBD, sphincteroplasty	1, well
8	Yes	Stones in gall bladder and common bile duct	Stones in common bile duct	Cholecystectomy, sphincteroplasty	24, well
9	Yes	Stones in common bile duct	Stones in common bile duct	Cholecystectomy, ECBD, T-tube, sphincteroplasty	15, well

ECBD, exploration of the common bile duct.

common bile duct was 8 mm. Stones were correctly identified in the common bile duct and gall bladder in two patients. Percutaneous transhepatic cholangiograms were performed in four patients and one child settled spontaneously after this procedure. Evidence of distal obstruction of the common bile duct was present in the other three (see figure).

Eight of the nine patients were subsequently explored and the diagnosis of IBPS (n=6) and gall stones (n=2) confirmed. Operative cholangiograms via the gall bladder showed abnormal entry of the common bile duct into the third part of the duodenum in two patients with IBPS. Details of operative findings, treatment, and follow up are given in table 3. Four patients with thick walled or oedematous gall bladders underwent cholecystectomy (both patients with stones and two with IBPS). The common bile duct was explored in seven patients, four had sphincteroplasties, one had a choledochoduodenostomy, and one had dilatation of the ampulla. Interestingly a normal gall bladder was found in one child with stones in the common bile duct. T-tube or cholecystostomy drainage was used in six patients. Postoperative cholangiography was used to exclude residual obstruction before removal of the drainage catheter or T-tube 10–21 days after surgery. Jaundice resolved in all nine patients and there were no postoperative complications. Patient follow up ranged from one month to two years with a mean of six months.



Percutaneous transhepatic cholangiogram showing dilated extrahepatic bile ducts secondary to inspissated bile plug in the distal common bile duct.

Discussion

Intraluminal biliary obstruction is a rare cause of jaundice in early life,[6 7] and the incidence may be estimated indirectly by a comparison with the 280 patients seen during the same time interval at this hospital with biliary atresia (incidence 1:15 000 live births).

Ladd described five patients with obstructive jaundice caused by a mechanical obstruction of the common bile duct by plugs of thickened bile.[8] He believed that the condition was secondary to distal common bile duct stenosis. Hsia *et al* investigated 156 infants with obstructive jaundice of whom 60% had biliary atresia.[9] Fifteen per cent had inspissated bile plug syndrome secondary to erythroblastosis fetalis and 19% had IBPS of unknown aetiology. It was thought that the syndrome was caused by a combination of factors that included small bile ducts, hepatic immaturity, dehydration, and thickened bile secretions. However, this group included patients with polycystic kidney disease and congenital hepatic fibrosis and this may have been a factor. Five patients of these patients with IBPS went on to develop cirrhosis.[10]

Haemolysis because of rhesus or ABO incompatibility was a significant factor in many of the early case reports,[1 11 12] and the development of early exchange transfusion as an effective form of treatment led to a sharp reduction in numbers. More recently the use of prolonged parenteral nutrition has been associated with IBPS,[13] cholestasis,[14 15] biliary sludge,[16] and gall stones.[17] It has been proposed that a tenacious, viscid bile occurs either as a result of parenteral nutrition or secondary to enteral failure. Blood tranfusion, dehydration, and diuretic treatment may cause an increase in the bilirubin/bile concentration leading to oversaturation.[2 18] Many of these infants have other problems such as prematurity, respiratory distress syndrome, necrotising enterocolitis, or intra-abdominal sepsis and intravascular coagulopathy.[4 13 14 19 20] Cystic fibrosis has also been implicated in the development of IBPS and cholelithiasis, particularly in small and premature infants.[21]

Lilly and Sokol considered that neonatal obstruction of the common bile duct in the absence of any of these factors was unusual.[6] In our seven patients with intraluminal biliary obstruction possible contributory factors included forceps labour (n=1), neonatal jaundice (n=1), blood transfusion (n=1), consanguinity, hypoglycaemia, and caesarean section (n=1), and hepatic haemangioma (n=1). Bruising after forceps or caesarean delivery can produce hyperbilirubinaemia after breakdown of blood and immature hepatocyte function may be responsible for an impaired conjugation of bile acids. Undetected haemolysis associated with the hepatic haemangioma may have caused bilirubin saturation of bile in one of our cases. All nine infants were boys, but no sex difference has been reported in the predisposition to intraluminal biliary obstruction.

Abnormalities of the extrahepatic biliary tree[22] and cholecystitis[23] have been associated with gall stone formation in children. Congenital anomalies of the lower common bile duct particularly anomalous pancreaticobiliary junctions have recently been described in cases of IBPS.[24] An abnormal entry of the lower common bile duct into the third part of the duodenum was demonstrated in two of our patients. Abnormal entry of the lower common bile duct may be associated with abnormal sphincter formation and function, and at operation the common bile duct was dilated secondary to a distal functional obstruction. No predisposing factors were found in two children. It may be difficult to exclude biliary atresia in this group of patients. Clinical examination (and testing of stool) may not differentiate between the two groups. Liver function tests confirm an 'obstructive' picture, but the concentration of conjugated bilirubin and alkaline phosphatase and γ-glutamyltransferase activities can be higher than expected for infants with biliary atresia. Radionuclide scans pointed to the diagnosis of biliary atresia, but it has been suggested that a repeat examination will show excretion in IBPS.[25]

Ultrasound scan was helpful in identifying a dilated extrahepatic biliary tree, biliary sludge/plugs and stones, although one patient with a common bile duct of 8 mm diameter was mistakenly diagnosed as having a choledochal cyst. Endoscopic retrograde cholangiopancreatography, although not performed in these patients, is now being assessed as a diagnostic test for biliary atresia.[26] In future it may identify patients with intraluminal biliary obstruction and anomalous junctions of the pancreaticobiliary ducts.

Liver biopsy specimens from infants in this series showed evidence of obstruction. The features (which included canalicular bile plugs, bile duct proliferation, and giant cell transformation) are non-specific, however, and represent a common type of response to bile duct obstruction in this age group. Other causes of conjugated hyperbilirubinaemia in the neonate include infection, metabolic disorders, or inflammatory disease of the liver.

A small number of patients with equivocal tests for biliary atresia come to laparotomy. At operation it is usually simple to differentiate between atresia and intraluminal biliary obstruction. Cholangiography is performed via the gall bladder to demonstrate the biliary tree. Brown has described successful irrigation of the common bile duct at surgery using a mucolytic agent, N-acetylcysteine, which has been used to reduce the viscosity of pulmonary mucus.[27] Endoscopic or percutaneous transhepatic cannulation and flushing of the common bile duct may therefore offer a satisfactory non-operative treatment for this condition. Cholecystectomy is recommended in children with thickened or inflamed gall bladders and gall stones within the gall bladder.

Gall stones are a rare cause of jaundice in infancy, but like IBPS the incidence appears to be increasing. The use of ultrasound to investigate children may account for some of this increase.[28] In a prospective ultrasound study of neonates receiving total parenteral nutrition, 44% were found to have biliary sludge and 5% developed stones.[29] Haemolytic anaemias are the commonest cause of gall stones in children, and most are 10 to 13 years old at presentation.[30] Other causes include ileal resection, Crohn's disease,[20] biliary tract anomalies,[5] and prolonged total parenteral nutrition and frusemide treatment.[2] The two patients reported in this paper were older (4 and 6 months) than our group with IBPS, but they were young in comparison to other reports of children with gall stones. Spontaneous resolution of both IBPS and gall stones has been reported.[31 32]

There appears to be a range of clinical problems associated with increased breakdown of bilirubin, failure of secretion, and oversaturation of bile, which presents with obstructive jaundice in the young child. Canalicular bile plugs and cholestasis represent the commonest response and appear to be reversible. Inspissated bile plugs in the extrahepatic biliary tree may represent the next stage and occasionally the child will develop stones.

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Compliance assessed by the Medication Event Monitoring System

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Abstract

The accurate assessment of patient compliance is especially crucial in evaluating the efficacy of a new treatment. Because of the problems associated with parenteral desferrioxamine, the development of a safe, effective, and convenient iron chelator is of high priority. The high morbidity and mortality associated with iron overload requires careful evaluation of the ability of any new agent to promote long term effective iron chelation. Patients' compliance with an orally available chelating agent, 1,2,-dimethyl-3-hydroxypyrid-4-one (L1), that has been demonstrated to induce in vivo iron excretion equivalent to that of desferrioxamine during supervised short term administration, was examined. Compliance was assessed in seven patients by patient inverview, by daily diaries reviewed monthly with each patient, and with the use of the Medication Event Monitoring System (MEMS) standard pill bottles with microprocessors in the cap that record the timing and frequency of bottle openings. L1 was dispensed in MEMS containers to the patients, who, unaware of their significance, recorded compliance using a daily diary. Overall compliance rate (% of prescribed doses taken) measured by MEMS was 88·7 ±6·8%. When 'doubling of doses' was accounted for, significantly poorer compliance with L1 was noted by MEMS (91·7±7·4%) than by patients' diaries (95·7±5·2%). There was no significant difference in patient compliance recorded between the first and last 30 day period of drug administration. MEMS can eliminate the confounding variable of erratic patient compliance in the evaluation of a new drug's efficacy. As MEMS cannot distinguish a missed dose from one doubled at the next bottle opening, the use of patient diaries is a useful adjunct to the accurate assessment of compliance and should be combined with the use of MEMS.

Evaluation of the therapeutic efficacy of a treatment regimen may be confounded by erratic patient compliance, the accurate assessment of which is especially crucial in demonstrating the benefit of any new treatment. The Medication Event Monitoring System (MEMS, Aprex Corporation, Fremont, California) standard pill containers with microprocessors in the cap, to record the timing and frequency of bottle openings, are a useful adjunct to estimates of compliance using patients' self reporting and/or pill counts.[1] Recently, we reported effective iron chelation with supervised short term administration of oral 1,2-dimethyl-3-hydroxypyrid-4-one (L1) in iron loaded patients poorly compliant with parenteral desferrioxamine.[2] Because of the high morbidity and mortality associated with tissue iron overload,[3] the ability of L1 to promote long term effective iron chelation in these pateints must be carefully evaluated. However, its therapeutic benefit may be negatively influenced by poor compliance in patients with a history of not taking their desferrioxamine as instructed.

Patients and methods

PATIENTS

Seven patients with transfusion dependent homozygous β thalassaemia began iron chelating treatment with oral L1. Four patients were started on L1 because of erratic compliance with nightly subcutaneous desferrioxamine treatment and three patients because of severe desferrioxamine neurotoxicity.[4] The mean (range) age of the patients was 17·4 (10–22) years. In five patients drug administration was self supervised; two sisters, age 10 and 12 years, were supervised by a parent. Before L1 treatment the patients had administered nightly subcutaneous desferrioxamine, with varying degrees of compliance, for a mean (range) period of 10·6 (8–12) years.

All patients, and the parents of the two children under 16 years, were aware of the importance of compliance with chelation treatment in the prevention of fatal iron related organ dysfunction. Written informed consent was obtained from each patient or parent at the time of initiation of L1 treatment. The experimental aspects of the drug administration and the lack of any alternative method of preventing and treating iron overload was emphasised. The nature of MEMS was unknown to the patients or parents, who also recorded compliance using a daily diary, reviewed on a monthly basis by one investigator. Patients were instructed to return all pill containers at their monthly visit at which time the remaining pills were counted.

Approval for the study was obtained from the Hospital for Sick Children human subjects' review committee.

METHODS

L1 capsules were dispensed in MEMS containers, which are standard size pill bottles fitted with a cap that contains a microprocessor.[1] Each bottle opening and closing was recorded as a presumptive dose. Data were retrieved

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monthly by connecting the container to a microcomputer communication port. Each battery operated cap collected up to 350 events between visits for data retrieval. Collected data were sent on a diskette to the Aprex Corporation for analysis. Information was provided as listings of the date and time of individual bottle openings and closings, the duration of opening, and the hours elapsed since the previous dose. Also provided were the ranges of dose intervals and the times doses were taken.

DOSAGE

Each patient was instructed to take L1 at eight hour intervals, and to supplement any missed dose at the time of the day's subsequent dose. Thus, if a patient doubled any dose, only one bottle opening was recorded. To adjust the dose to 75 mg/kg/day, five patients administered L1 at two capsule strengths (300 mg and 600 mg capsules) at different dosing frequencies; two patients administered one capsule strength only (300 mg capsules). For example, one patient administered two 600 mg capsules three times daily, and one 300 mg capsule one time daily; both regimens were recorded by diary and the MEMS device. Dosing patterns therefore included three times a day in four patients, and three times a day plus once daily in three patients.

ASSESSMENT OF COMPLIANCE

For the purposes of this analysis, only the omission of doses was considered as true non-compliance with L1 treatment. Conversely, the doubling of a missed dose of L1 at the time of the day's subsequent dose, as instructed, was not considered as non-compliance. The number of days during which delays of over 60 minutes in drug administration was also recorded. As failure to comply with the once daily regimen was likely to be reflected in the three times a day regimen, only the latter was included in the calculations of compliance.

STATISTICAL METHODS

Data are presented as mean (SD). Mean values were compared by paired Student's *t* test as appropriate.

Results

The *compliance rate*, calculated as the percentage of prescribed doses taken, as estimated by MEMS, was 88·7 (6·8)%. When allowance was made for supplementation of a missed dose at the time of the subsequent dose, a compliance with L1 increased to 91·7 (7·4)%. The corresponding figures for percentage of days that the correct number of doses were taken were 71·6 (15·1)% and 79·9 (18·2)% respectively.

Despite the importance of taking their medication at regular intervals having been explained, patients often delayed taking their L1, with delays greater than 60 minutes occurring more than half of the time (55·6 (25·8)% of total days observed).

Patients' diaries reported a compliance rate of 95·7 (5·2)% of prescribed doses taken. This form of self monitoring lead to a significantly greater estimation of compliance compared with MEMS which yielded a corresponding value of 91·7 (7·4)% ($p=0·039$).

Compliance was also assessed by pill counts (calculated as [number of missing pills/number of pills prescribed for the interval] × 100%). No differences were noted in the evaluation of compliance by pill counts (95·7 (4·8)%) as compared with that by MEMS (91·7 (7·4)%).

Overall, compliance with treatment was not significantly different during the first month of L1 treatment when compared with the last (fourth) month, when missed doses were considered.

Discussion

Because of the difficulties associated with administration of nightly subcutaneous desferrioxamine for the treatment of iron overload,[4] a convenient and non-irritating substitute for desferrioxamine, in the form of an orally available iron chelating agent, has been sought for many years. Until recently this search has been unsuccessful. However, recently we[2] and others[5] have demonstrated the short term efficacy of L1 in patients with iron overload. This treatment cannot be extended to all patients with iron overload until its long term efficacy and safety are demonstrated.

Presently, iron excretion in a cohort of patients with poor or erratic compliance with desferrioxamine is being evaluated. In general, demonstration of efficacy of any new agent is confounded when patients do not adhere to prescribed regimens.[6] In this particular instance the potential benefits of L1 must be evaluated in a cohort of patients whose compliance with treatment has already been demonstrated to be erratic. We have reported a significant decline in compliance with a regimen of nightly subcutaneous desferrioxamine between the ages of 10 and 20 years, frequently resulting in fatal iron accumulation.[7] Because of the high morbidity and mortality associated with tissue iron overload,[3] the ability of L1 or any new agent to promote long term effective iron chelation must be carefully evaluated.

In the evaluation of patient compliance, three different measures have been utilised: self reports, collateral reports, and objective measures.[8] The inaccuracies in self reports of health related behaviour have been extensively reviewed.[9] Self reports are plagued by failure of memory, misunderstanding of treatment recommendations, and differences in internal standards of evaluations of behaviour.[8] Purposeful omission of the truth to avoid recrimination, embarrassment, or rejection by the prescribing physician[10] is also a major contributor to errors in self reporting of compliance.[11 12]

Collateral reports of compliance include reports of physicians, nurses, other health professionals, friends, and family members. The accuracy of collateral reports is a function of familiarity with the patients.[13] In general, medical practitioners' ratings of their patients' compliance tend to be grossly inaccurate;

physicians have been shown to routinely overestimate their patients' compliance and to be unable to distinguish compliant and noncompliant patients.[14]

Objective measures of compliance include pill counts and urine or blood assay of the drug or its metabolites. Pill counts can be confounded if unused bottles are mislaid or deliberately not returned. The taking of occasional pills can balance with days of missed pills to provide an erroneous impression of adherence.[15] Serum or urine concentrations of the drug are most useful for compounds with long half lives because results provide an approximation of use during the preceding week or longer. For rapidly cleared drugs, brief intake before the test can result in adequate concentration, erroneously suggesting regular medication use.[1]

The ideal standard of compliance measurement should be simultaneously unobtrusive (to avoid patient sensitisation and maximise cooperation), objective (to produce discrete and reproducible data for each subject), and practical (to maximise portability and minimise cost).[16] MEMS, a novel method used in our study, can measure adherence to a treatment regimen on a daily and hourly basis and is minimally intrusive to the ambulatory outpatient. MEMS has been reported as useful to study compliance with prescribed regimens and to compare results with other traditional measures.

In the present study, we have used MEMS to evaluate compliance with a new treatment in patients, of whom some were known to be previously poorly compliant with a regimen of nightly subscutaneous desferrioxamine. As previously noted, compliance is reduced when the treatment regimen is complex, of long duration, dependent on an alteration of the patient's lifestyle, inconvenient, or expensive.[17–20] Frequency of dosing in one study was a more important factor for compliance than the number of different medications taken at each dosing interval.[21] Frequent (three to four times daily) dosing, a requirement with L1, would therefore be expected to increase inconvenience and diminish compliance.

In the present study, patients' diaries reported a compliance rate higher than that recorded with MEMS. In contrast, for the same regimen, compliance as measured by MEMS was significantly less at 91·7 (7·4)% of doses taken. Our findings of consistent over reporting of compliance confirms previous suspicions that, in the absence of objective measures of compliance,[11] patients will exaggerate the degree of their compliance with a treatment regimen, perhaps to gain acceptance, support, or approval from the prescribing physician.[12] The use of patients' diaries does eliminate to a degree the confounders of memory failures in compliance reporting.[6] In addition, because patients were instructed to double any missed dose of L1 at the subsequent one, the adjunctive use of patients' diaries was necessary to distinguish lack of compliance with a dose of L1 from one doubled at the next presumptive dose while using MEMS.

Estimation of compliance by pill counts (95·7 (4·8)%) was identical to MEMS. With the continuation of this study the role of pill counts will need to be further examined to determine if, over time, they will provide a satisfactory alternative to the more expensive MEMS monitoring.

Overall, compliance with treatment was not significantly different in the first month of L1 treatment when this was compared with the last month when missed doses were considered. The importance of the *duration* of a regimen in compliance with treatment is highlighted by a study that found a 30% incidence rate of dosage errors in patients with diabetes for one to five years, but an 80% dosage error rate in patients who had the disease for over 20 years.[22]

Despite its obvious advantages, MEMS still does not provide a foolproof method of compliance assessment. In the same way that it must be assumed that a bottle opening means the drug was ingested, it must be assumed that the absence of a bottle opening means the dose was not taken. These conditions, however, may not always hold true. For example, patients not wishing to carry their pill bottles with them may remove several doses at one time (thus registering only one bottle opening), yet still take their medication according to their prescribed schedule. This scenario is most likely to occur when the patients are unaware that their compliance is being monitored and are unaware of the nature of the MEMS container, as in the present study.

Our study focused on patients' compliance. However, generally drug trials are analysed by 'intention to treat', as compliance or lack of compliance is part of the assessment of the usefulness of a drug in clinical practice. However, even in the larger context of 'intention to treat', accurate analysis of patients' compliance is crucial.

Our study demonstrates that MEMS is a useful aid in quantifying patients' compliance during the evaluation of the therapeutic efficacy of a new drug. In the evalution of a new drug it is crucial to establish appropriate compliance before one can reject the agent as ineffective. As MEMS cannot distinguish a missed dose from one taken (that is doubled) at the next bottle opening, the use of patients' diaries should be a useful adjunct to this method of assessment of compliance.

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Can cleaning carpets cause Kawasaki's curious clinical conglomerate? Colorado case-control comparison corroborates contentious connection

It stands to reason, doesn't it, that a disease like Kawasaki disease can't be due to something as simple as carpet cleaning; it's as silly as saying that something like pink disease could have been caused by teething powers or Reye's syndrome associated with giving aspirin. The suggestion about Kawasaki disease (I shall continue to call it a disease because it trips more lightly off the tongue, though I recognise the case for calling it a syndrome) was first made in Colorado in 1982[1] but several subsequent studies failed to confirm the association. Now workers in Denver have resurrected the idea (Alan M Rauch and colleagues, *Pediatrics* 1991;87:663–9).

The largest epidemic of Kawasaki disease yet reported in the United States occurred in an area to the east of the Rocky mountains centred on Denver between October 1984 and January 1985. There were 62 cases in all, of whom 52 lived in the Denver metropolitan area. The case-control study included 26 patients. Controls matched for date and place of birth, race, and sex were selected at random from birth certificate records and a questionnaire was administered by telephone to the parents of patients and controls. The age range of the children was 3 months to 12 years with nearly 90% younger than 5 years. The incidence was significantly higher in blacks than in whites and highest of all in Asians (origin unstated). Carpet cleaning must be a popular activity in Denver because 62% of the patients and 20% of controls lived in homes where rugs or carpets had been cleaned within 30 days of the onset of the illness ($p<0{\cdot}01$, odds ratio 5·0, 99% confidence interval 1·1 to 23·1) though the study rules stated that the area cleaned might be as small as 1 foot in diameter and the cleaning fluid might be a commercial cleaner or soap and water. Data from 35 patients in three studies suggested exposure to carpet cleaning in the period from 13 to 30 days before the onset of the illness in 33 and 0 to 12 days in two ($p=0{\cdot}00005$).

Other associations were looked for. It has been suggested that living near a body of water might predispose to the disease. In this study the median distance from a body of water (ditch, creek, or pond) for patients was 200 yards and for controls 500 yards ($p=0{\cdot}06$). No significant differences were found for antecedent illness in the child, illness in the family, parental income, and a list of 18 other factors.

It's odd, isn't it? Could the results be explained by recall bias? If so, why the clustering in the period between 13 and 30 days before the onset of the illness rather than more recently? There seems to be no chemical or toxic explanation. The authors suggest that an infectious agent might be stirred up by the cleaning and agitation of the carpets. The possible association with living near water could also suggest a small animal reservoir or an insect vector.

These studies must be telling us something, but what?

ARCHIVIST

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[1] Patriarca P, Rogers M, Morens D, *et al*. Kawasaki syndrome: association with the application of rug shampoo. *Lancet* 1982;ii:578–80.

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Impaired pubertal growth in acute lymphoblastic leukaemia

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Abstract

The growth of 182 patients who were long term survivors of childhood acute lymphoblastic leukaemia was retrospectively analysed. All remained in first remission and were treated with either 1800 or 2400 cGy of cranial irradiation. None had been treated with either testicular or spinal irradiation. Ninety three (51 boys, 42 girls) were treated with 2400 cGy and 89 (42 boys, 47 girls) were treated with 1800 cGy cranial irradiation. All patients were treated with standard chemotherapy including intrathecal methotrexate in similar dose regimens in either group. Mean age (SD) at diagnosis in the group treated with 2400 cGy was 4·8 (2·6) years and mean age in the group treated with 1800 cGy was 6·5 (3·3) years. Mean height SD score at diagnosis in the 2400 cGy group was +0·29 and final height achieved was −0·63. Mean height SD score at the start of treatment in the group treated with 1800 cGy was +0·40 and mean final height was −0·53. There was a similar reduction in height SD score in both groups during the pubertal growth spurt.

The decrement in height SD score was greater when treatment was administered at less than 7 years of age in either dose regimen, both in prepubertal and pubertal growth. However, the decrease in height SD score was found to be greater in girls than boys. There was a trend in both sexes for the onset of puberty to be at a younger age with a lower treatment dose of radiotherapy. However, in girls treated with the lower dose regimen there was a significant reduction in the mean age of onset of puberty which was 9·9 years. Our data suggest that girls treated at less than 7 years of age have a severe impairment of pubertal growth, which is probably a combination of the dual endocrinopathy of premature puberty and growth hormone insufficiency.

Long term survival for children with acute lymphoblastic leukaemia has improved enormously in recent years, partly due to the introduction of treatment to the central nervous system,[1] [2] which is given as a combination of intrathecal methotrexate and cranial irradiation.[3] Because of the morbidity of cranial irradiation, the dose administered has been reduced in recent years from 2400 cGy in 15 fractions over three weeks to 1800 cGy in 10 fractions over two weeks.[4]

Cranial irradiation may cause pituitary dysfunction, of which growth hormone insufficiency is the most common endocrinopathy. This is related to both the administered dose of irradiation and the method of fractionation.[5] [6] The effect of the irradiation is delayed and progressive. It has been reported that regimens of low dose cranial irradiation may cause growth hormone insufficiency and growth failure[7] [8] in children with acute lymphoblastic leukaemia. The degree of growth suppression and whether this requires growth hormone replacement treatment has been controversial.[9] [10] Recent data have even suggested that final height is not altered in children treated for acute leukaemia.[11] Low dose cranial irradiation in children with acute lymphoblastic leukaemia has been reported to be associated with central premature and precocious puberty,[12–14] predominantly affecting girls.[15] However, the significance of this for ultimate height is unknown.

Between 1970 and 1980 the dose of cranial irradiation administered was 2400 cGy but this was superseded in 1981 by a dosage of 1800 cGy. During the last 20 years treatment has altered in that induction and consolidation has become more intensive. However the basic drugs used, including intrathecal methotrexate and maintenance treatment (6-mercaptopurine, methotrexate, prednisolone, and vincristine), have essentially remained unaltered. We have been able to compare the onset of puberty and the pubertal growth spurt in children treated by either of these two irradiation dose regimens.

Patients and methods

PATIENTS

Data from 182 patients were analysed in this study from a total cohort of 307 patients who were survivors of acute lymphoblastic leukaemia diagnosed at the Hospital for Sick Children between 1970 and 1986.[16] All patients were in first remission, had been off treatment for two years or more, and had attained the onset of puberty at the time of this study. None had received gonadal or spinal irradiation. Twelve children (seven treated with 1800 cGy, five treated with 2400 cGy) were treated with growth hormone and/or gonadotrophin releasing hormone (GnRH) analogue during the course of this study and were excluded, as well as those with dysmorphic syndromes or abnormal karyotypes.

Ninety three patients (51 boys, 42 girls) were treated with 2400 cGy cranial irradiation and 89 (42 boys, 47 girls) were treated with 1800 cGy. Cranial irradiation was usually given within eight weeks of diagnosis or occasionally delayed until the patient was 2 years of age. Chemotherapy regimens have been previously

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described.[17–19] The numbers of patients at diagnosis, onset of puberty, and final height are indicated in fig 1. Because the group treated with 2400 cGy was before 1980, a much larger number of patients had attained final height than in the lower dose group.

METHODS

Clinical records of the patients were examined retrospectively including height obtained at diagnosis (equivalent to the onset of treatment), the onset of puberty, and final height. Stature was expressed as SD scores with comparison of data from Tanner *et al.*[20 21] No adjustment was made for secular trend in height. The onset of puberty was taken as the acquisition of breast development in girls (B2) and the development of either stage 2 genitalia and/or 4 ml testicular volume in boys. Normal data for the ages of attainment of sexual maturation were from Marshall and Tanner.[22 23] The patients were divided into two groups according to the two dose regimens of cranial irradiation used as well as the age at onset of acute lymphoblastic leukaemia. Statistical measurements were performed using paired and independent *t* test.

Results

Data for change of height SD score during puberty are shown in fig 1. The pattern of reduction of height SD score during both prepuberty and puberty was similar in both groups. However, this was not significant in the 1800 cGy irradiation group, which probably reflects the smaller proportion of patients who had attained final height. Age at onset of puberty was greater by 0·4 years in the children treated with the higher dose regimen but this may be a reflection of a secular trend.

The decrement in height SD score, especially during puberty, was greater when cranial irradiation was administered at less than 7 years of age in both dose regimens (fig 2). In contrast, children treated for acute lymphoblastic leukaemia at the age of 7 years or above were more

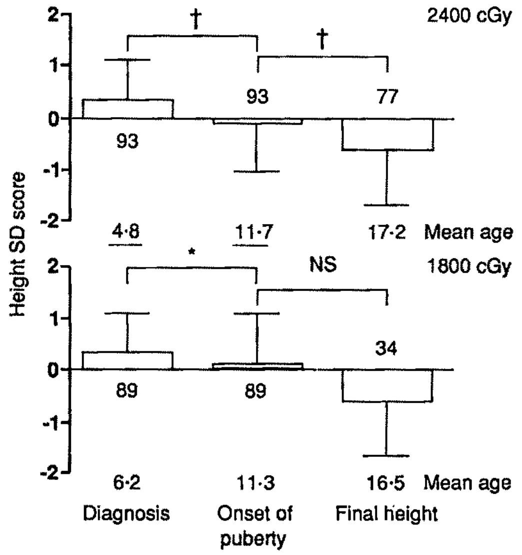

Figure 1 Growth data for 182 children treated for acute lymphoblastic leukaemia with either 2400 or 1800 cGy cranial irradiation. Height SD score at diagnosis, at the onset of puberty, and at final height are shown. Horizontal bars represent 1SD. *=$p<0{\cdot}005$, †=$p<0{\cdot}0001$, *NS=not significant. The number of patients are indicated.*

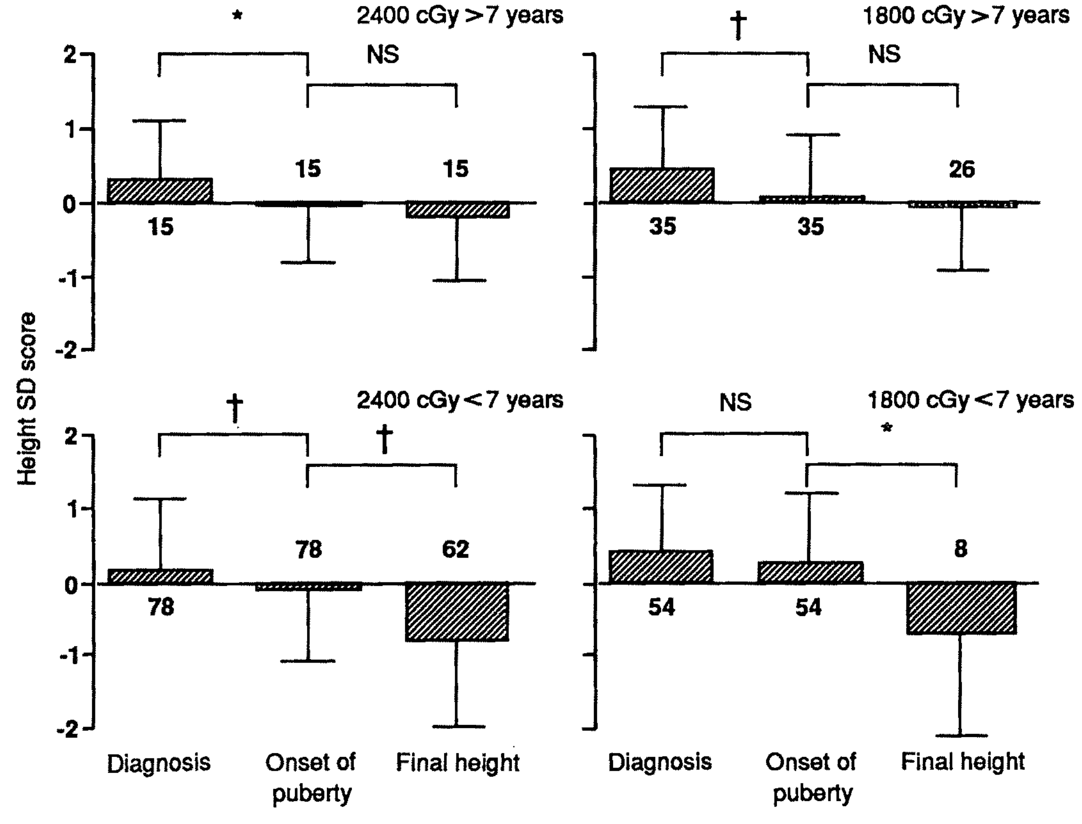

Figure 2 Height SD score in 182 children with acute lymphoblastic leukaemia treated with cranial irradiation (2400 cGy or 1800 cGy), before and after 7 years of age. Horizontal bars represent 1SD. *=$p<0{\cdot}005$, †=$p<0{\cdot}0001$, *NS=not significant. The number of patients are indicated.*

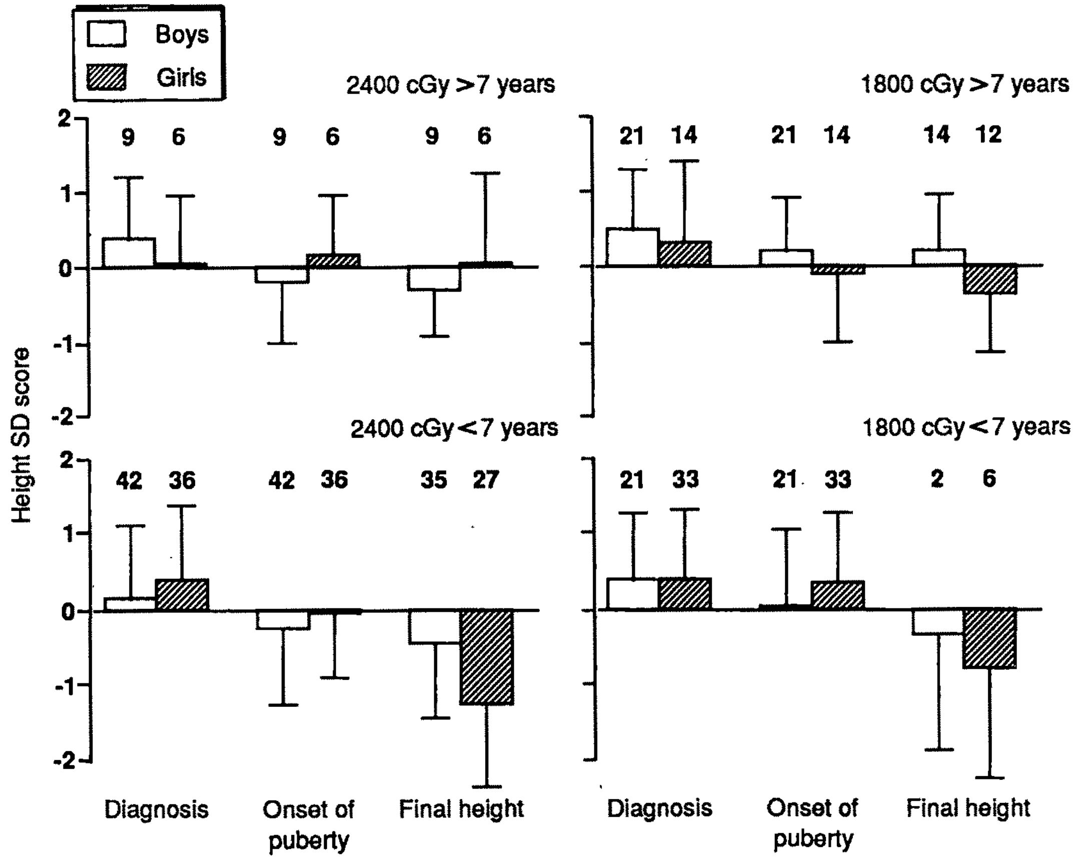

Figure 3 Height SD score in 93 (51 boys, 42 girls) and 89 (42 boys, 47 girls) patients treated for acute lymphoblastic leukaemia with 2400 cGy and 1800 cGy cranial irradiation respectively, before and after 7 years of age. Horizontal bars represent 1SD. The number of patients are indicated.

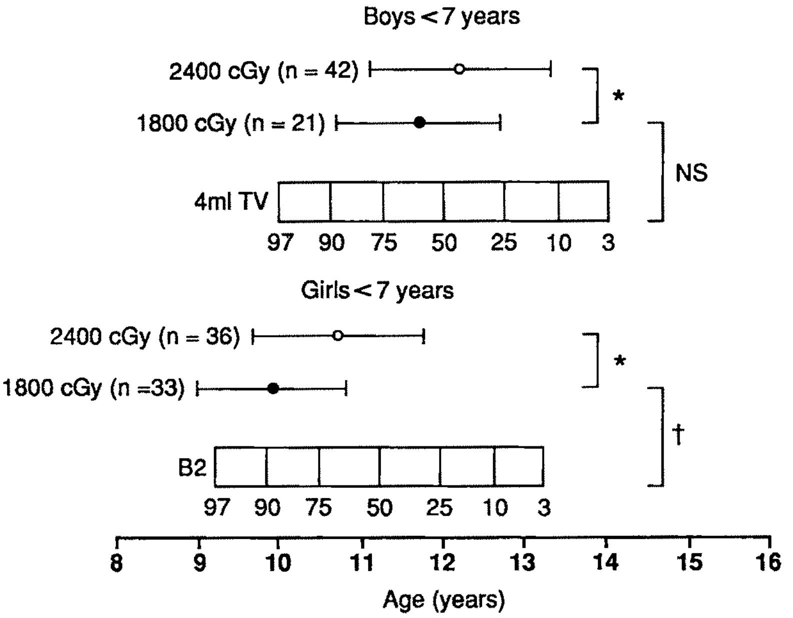

*Figure 4 Age at the onset of puberty in 69 girls (B2) and 63 boys (4 ml testicular volume) treated for acute lymphoblastic leukaemia under the age of 7 years with either of two dose regimens of cranial irradiation (2400 or 1800 cGy). Vertical bars represent 1SD. Data for normal girls and boys from Marshall and Tanner 1969[22] and 1970[23] respectively. *=p<0·001, †=p<0·0001, NS=not significant. B2, breast stage 2; TV, testicular volume.*

affected during prepubertal growth in both irradiation groups. Differences between height SD score at onset of puberty and final height were not significant (fig 2). Girls were more affected than boys in both dose regimens, but the number of patients in each group attaining final height was small (fig 3).

In order to study the effects of cranial irradiation on pubertal development, we have excluded children treated for acute lymphoblastic leukaemia at greater than 7 years of age. Mean age (SD) at onset of puberty in the 2400 cGy group was 12·2 (1·0) years in boys and 10·6 (1·0) years in girls. By contrast, mean age at onset of puberty in the 1800 cGy group was 11·4 (1·5) years in boys and 9·9 (0·9) years in girls (fig 4). Surprisingly the onset of puberty with the lower dose was earlier in both sexes ($p<0·01$), and a significant difference was found in comparison with the mean of the British population for girls ($p<0·0001$), but not for boys.

Discussion

The main difficulty in the interpretation of this study arises from the fact that we have compared different treatment groups from 1970 until 1986, and this study is in series and not in parallel. No adjustment has been made for secular change in either stature or for the timing of puberty. However we believe that, even considering these difficulties, our data are relevant. Furthermore the exclusion of 12 patients who received endocrine treatment for growth failure increases the significance of our findings. Broomhall and colleagues demonstrated in a large number of patients that children with acute lymphoblastic leukaemia were significantly taller than the normal population with a mean SD score of +0·49.[24] We found that at diagnosis our patients were taller than average. A possible explanation is that leukaemia is a disease of the higher social classes and the latter have greater than average stature.[25]

It is appreciated that the treatment of brain tumours with high dose cranial irradiation is associated with a high incidence of growth hormone insufficiency/deficiency.[5] In our data the decrement in final height was similar with both 2400 cGy and 1800 cGy cranial irradiation. Our observations are in agreement with Shalet in that the initial endocrinopathy associated with cranial irradiation is growth hormone insufficiency.[5] It has been reported by previous authors that growth hormone secretion in young children is more sensitive to damage by a given dose of irradiation than in older children.[26] The effects of irradiation on pituitary function tend to be delayed and progressive over several years.[5] Certainly children treated with cranial irradiation under the age of 7 years have a higher incidence of growth failure than older children[26 27] and our data are in agreement with this.

Cranial irradiation of either 2400 or 1800 cGy affects growth in prepuberty as well as in puberty. In normal children growth in prepuberty is a continuous deceleration, and there is evidence of a progressive decrease in growth hormone secretion until the onset of the growth spurt.[28] During the pubertal growth spurt growth is dependent on both sex steroids and growth hormone and one without the other produces an inadequate growth acceleration.[29] It has been suggested that growth hormone secretion in children treated with low dose cranial irradiation is predominantly decreased during puberty rather than prepuberty.[30] Our data suggest that overall, prepubertal growth is affected almost as much as pubertal growth, but when the groups were subdivided by age, a different picture emerged. There was a significant decrease in height SD score between the onset of puberty and final height attainment in both radiation groups diagnosed under the age of 7 years, but not during prepubertal growth in the 1800 cGy group. This suggests that the larger dose of 2400 cGy affected both prepubertal and pubertal growth but 1800 cGy given at a young age predominantly caused loss of the growth spurt. Of course, the majority of the population with leukaemia are diagnosed under the age of 7 years and indeed in this study the onset of leukaemia was below this age in 72% of the children. The latter situation of impairment of the pubertal growth spurt in those children receiving 1800 cGy at less than 7 years of age will thus be the commonest prevailing picture at the present time.

Recent data have suggested that low dose cranial irradiation is associated with precocious or early puberty in girls rather than boys and our present analysis support this. Of interest from our study is the suggestion that earlier puberty is the result of the lower dose regimen of 1800 cGy rather than 2400 cGy cranial irradiation. Certainly early puberty could be a contributory reason as to why growth impairment in the girls was greater than in the boys. Alternatively it may also be that growth hormone secretion is more adversely affected in girls than boys in the same way that gonadotrophin secretion is affected differently between the sexes. We know no other supportive data for such a hypothesis. The most important single group to identify therefore is girls treated at a young age as they show the greatest degree of growth retardation. As well as the possibility of growth hormone treatment for this group, it may be advantageous to therapeutically manipulate the timing of pubertal maturation using a GnRH analogue. There is now some evidence to suggest that a combined regimen of both growth hormone and GnRH analogue may be advantageous.[15]

In conclusion, we suggest that all children who are treated for acute lymphoblastic leukaemia with cranial irradiation, especially girls treated at a young age, have their growth carefully monitored both during prepuberty and especially during puberty. Certainly the growth failure induced by cranial irradiation at a low dose regimen may be significant and require appropriate treatment. Our data indicate which groups of children by age and sex are likely to require special attention.

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. . . and while on the subject

Accepted treatment for Kawasaki disease is with aspirin and intravenous gammaglobulin. An American multicentre randomised trial reported in 1986 showed that coronary artery dilatations were less common after treatment with gammaglobulin and aspirin than after aspirin alone.[1] In that trial the gammaglobulin was given as four consecutive daily doses of 400 mg/kg body weight. Now the same workers have shown that a single infusion of 2g/kg is equally if not more, effective (Jane W Newburger and colleagues, *New England Journal of Medicine* 1991;**324**:1633–9). Clinical and laboratory indices of inflammation also resolved quicker with the single large dose.

An editorial in the same issue of the journal points out that there are still unresolved questions.[2] The main end point in these trials has been coronary dilatation of any severity seen on echocardiography. Dilatation of less than 6 mm is apparently relatively benign and it is the giant aneurysms which lead to myocardial infarction and death. The effect of gammaglobulin on mortality is not known. Nevertheless in the most recent trial none of the 254 children who had normal coronary arteries when first seen and who received the single large infusion of gammaglobuin developed giant aneurysms. All of the patients in this study were treated within 10 days of the onset of the disease. The effect of treatment later in the course of the disease in unknown but it seems reasonable to treat if the disease process is still active.[2]

The role of aspirin is uncertain. Continuous low dose aspirin seems indicated if there is persisting coronary abnormality but whether initial high dose treatment is necessary is not known.

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Frequent symptoms after DTPP vaccinations

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Abstract

A prospective study of minor reactions after the four combined vaccinations for diphtheria, tetanus, pertussis, and poliomyelitis (DTPP) was performed in 540 infants in the Netherlands. An analysis was made of the symptoms observed by the infants' parents after 2026 inoculations. The aim was to assess the frequency, association, and risk of recurrence of minor reactions. These were designated as fever (≥38·0°C), local reactions, crying, and other general symptoms (changes in sleeping or eating patterns, vomiting, drowsiness, fretfulness). Fever occurred after 67·7% of inoculations, one or more local reactions after 66·2%, and increased crying after 64·4%. After 80% of inoculations, one or more other general symptoms occurred. Only 4·4% of inoculations were followed by no minor reaction. Fever rarely occurred as an isolated symptom; it showed a significant association (i) with one or more local reactions, (ii) with increased crying, and (iii) with two or more other general symptoms. Chances of fever, redness at the inoculation site, and crying after inoculation increased with repeat inoculations if these reactions had occurred after preceding inoculation(s).

Since 1962 infants in the Netherlands have been vaccinated four times intramuscularly with a combined vaccine against diphtheria, tetanus, pertussis, and poliomyelitis (DTPP).[1] Injections are given at a minimum of three, four, five, and 11 months. The vaccine is prepared by the National Institute of Health and Environmental Protection (RIVM, Bilthoven). It contains diphtheria and tetanus toxoids, whole cell pertussis vaccine, and inactivated poliomyelitis vaccine in a medium containing aluminium phosphate. Administration occurs with the parents' permission and mainly at child health centres.

Frequent non-serious symptoms, known as minor reactions, and less common serious symptoms, the so called major reactions, are the undesirable side effects of these vaccinations.[2 3] This paper reports on a prospective study of symptoms of the first type. It pays particular attention to four categories: fever, local reactions, crying, and other general symptoms within 48 hours after inoculation.

The aim of the study was to answer three questions:

(1) How frequently do minor reactions occur after DTPP vaccinations among healthy infants in the Netherlands?

(2) Is there an association between the different minor reactions that occur?

(3) How great is the risk of recurrence of minor reactions after subsequent DTPP inoculation?

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Subjects and methods

STUDY POPULATION

A written request was sent to the parents of infants sequentially born between 1 March 1987 and 1 March 1988 in two medium sized towns (Amstelveen and Amersfoort) to participate in a study of the side effects of the four inoculations of the combined DTPP vaccine. The vaccinations were administered at 15 child health centres by physicians or nurses who knew the details of the study. Only infants who met the following conditions were enrolled into the study: birth weight not less than 2000 g; not suffering from neurological or internal diseases or defects; no fever (<38·0°C) at the time of inoculation; and at least one parent/guardian with adequate knowledge of Dutch.

METHODS

Parents who agreed by reply card to participate (62% of the parents asked) were visited at home by one of the two investigators (PLV, JTW) before the first vaccination. A number of data were collected at the visit (date of birth, birth weight, sex, general health). The observation forms were supplied in quadruplicate. The parents received a digital thermometer (Philips 5312M) and a transparent plastic ruler which measured the diameter of any redness at the injection site. The written information was also explained verbally.

The period of observation for each vaccination was four days, starting from the day before vaccination (day 0), the day of the vaccination (day 1), and the two subsequent days (day 2 and day 3). Day 0 served as a day of reference. Rectal temperature and any redness at the injection site were measured during four timed intervals per day (in the morning before the injection, 0–3 hours after the injection, 3–8 hours after the injection, and depending on the time of injection, in the evening). Further measurements were taken as the child's condition warranted.

On each observation day questions were also asked about the occurrence of swelling and pain at the injection site, about crying, and other general symptoms (changes in sleeping or eating patterns, vomiting, drowsiness, and fretfulness). Finally, data were collected on the time of vaccination, injection site, and use of any drugs.

After completion, the parents returned the observation form in a stamped, addressed envelope. Before DTPP4 the parents were telephoned. They were asked about the child's health and were reminded of their participation in the study.

After the forms were returned, the data were coded and entered into a computer. They were processed and analysed statistically with the use of the BMDP program. The association between minor reactions were tested by the χ^2 test for a 2×2 table and by the χ^2 test for trend in proportions. The risk of recurrence was assessed by multiple logistic regression analysis.

Results

There were 540 infants in the study, and 2026 complete and usable forms were returned (94% of the possible maximum). Four children were inoculated with DTPolio or with half doses of DTPP after a strong reaction to the previous vaccination. These forms have been excluded from the analysis. In 15 cases a fever (⩾38·0°C) was recorded before inoculation. These forms have also been excluded from the analysis. In 15 cases, infants received a measles, mumps, and rubella vaccination with the fourth DTPP vaccination (in different limbs). These forms were not excluded because these two different vaccinations do not interfere with each other. None of the participating children experienced convulsions, collapse, or encephalopathy.

FREQUENCY OF MINOR REACTIONS

One or more minor reactions were recorded by the parents after more than 95% of inoculations. Only 4·4% of inoculations were followed by no observable reaction. Table 1 lists the frequency of minor reactions observed on days 1, 2, and 3 (fever, local reactions, crying, and other general reactions) after each of the four DTPP vaccinations.

Fever ⩾38·0°C occurred after 67·7% of inoculations, high fever ⩾39·0°C after 9·9%, very high fever ⩾40·0°C after 0·6%. A fever of ⩾40·5°C was measured in three cases.

One or more local reactions occurred after 66·2% of vaccinations. A red area with a diameter exceeding 2 cm occurred in 19·3% of cases; after 2·5% of inoculations this red area had a diameter exceeding 8 cm. Redness, swelling, and pain occurred together after 12·4% of inoculations.

Table 1 Summary of minor reactions after four DTPP vaccinations, in percentages, per inoculation

Minor reactions	*DTPP1 (n=536)*	*DTPP2 (n=523)*	*DTPP3 (n=501)*	*DTPP4 (n=466)*	*Total (n=2026)*
Temperature					
38·0–38·9°C	58·4	57·2	53·3	62·7	57·8
⩾39·0	7·1	9·8	8·3	14·8	9·9
Local reaction					
Redness >2 cm	19·4	16·1	13·0	29·6	19·3
Swelling	31·7	32·7	31·1	44·6	34·8
Pain	56·2	55·8	48·5	73·0	58·0
Crying					
Increased	62·1	67·1	56·9	71·9	64·4
Inconsolable					
1–3 hours	11·8	12·8	8·8	7·7	10·4
⩾3 hours	2·4	3·2	2·4	2·4	2·6
Other general symptoms					
Sleeping changes	65·7	66·3	59·9	65·5	64·4
Eating changes	35·6	36·3	27·7	46·6	36·4
Vomiting	8·2	10·3	7·4	7·3	8·3
Drowsiness	29·1	30·0	26·5	43·6	32·0
Fretfulness	37·7	41·7	37·5	54·3	42·5

Increased crying occurred after 64·4% of inoculations. In 13% of cases inconsolable crying occurred for more than one hour. After 80% of inoculations, one or more other general symptoms occurred. The most common reaction was a change in sleeping pattern. Excessive sleeping occurred much more frequently than sleep loss. A change in eating pattern generally meant eating less than usual.

Reactions by series number

Reactions were more frequent after the fourth inoculation (DTPP4) than after any of the preceding inoculations (see table 1). Differences in fever and local reactions were most marked. Also, reactions were generally stronger after the fourth inoculation. After DTPP4, 77·4% of children had a rectal temperature of 38·0°C or higher, while this was true for an average of 64·7% after the three preceding inoculations. After DTPP4 a temperature of 39·0°C or higher was measured in 14·8% of the children; after the three preceding inoculations the average was 8·4%.

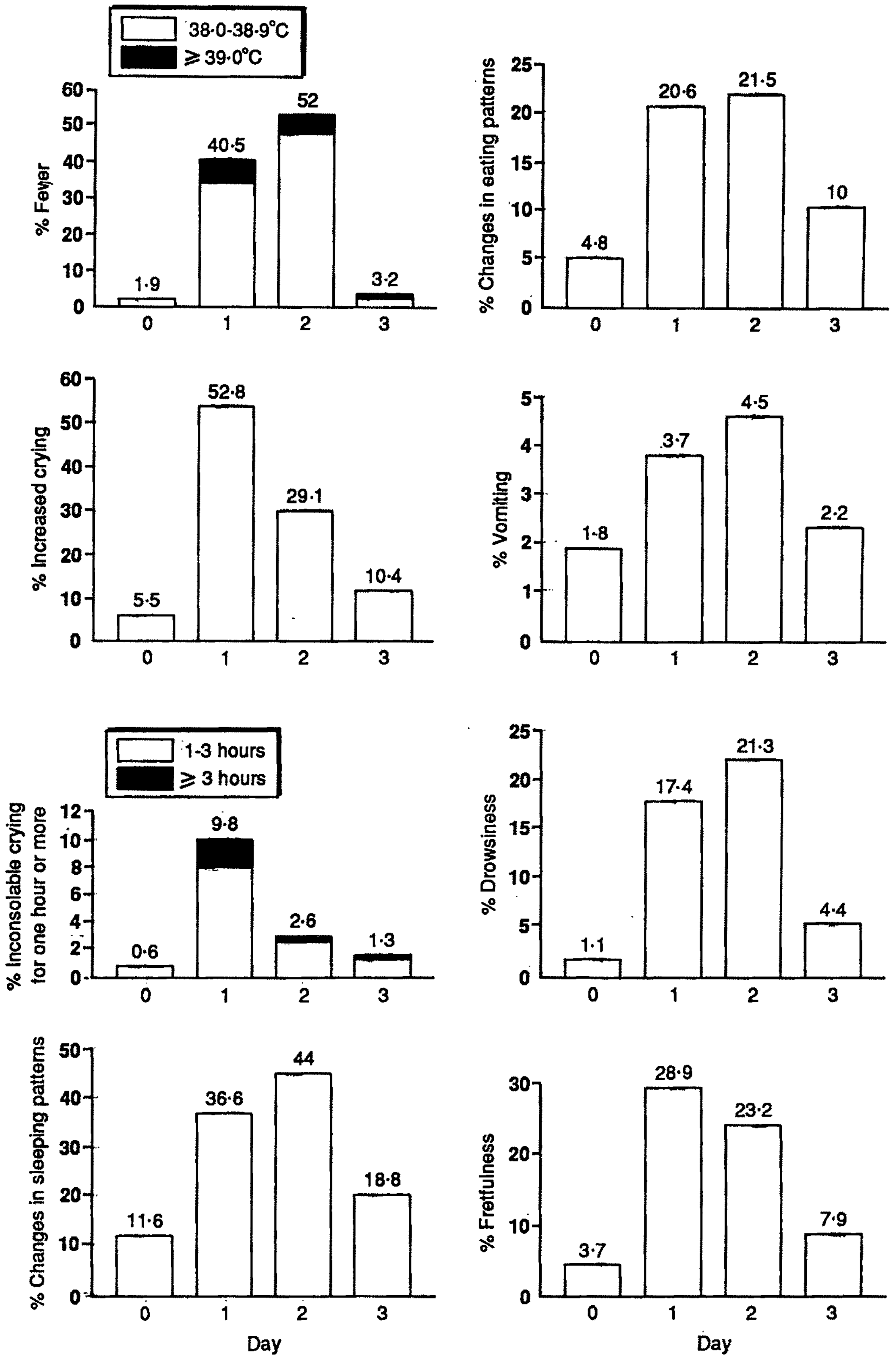
The fewest reactions generally occurred after DTPP3. It was of note that the time at which local reactions started varied per series number. Later inoculations were followed by a later onset of reactions. After the first inoculation 92·3% of redness reactions started on the day of inoculation (day 1); after the fourth, only 57·2%. To a small degree the same pattern could be seen with swelling and pain.

ONSET AND DURATION OF MINOR REACTIONS

Minor reactions often started on day 1 (day of vaccination) or day 2, and generally disappeared by day 3. If children reacted with fever, it began within 24 hours of the inoculation in more than 91% of cases. If a swelling or a red area (>2 cm) developed at the injection site, more than three quarters of these reactions began on day 1. Pain also began on day 1 in more than 90% of cases. The onset of increased crying was in 82% of cases on day 1; for inconsolable crying lasting more than three hours this percentage was 77·4%. Other general symptoms began on day 1 in more than half of the cases.

The figure demonstrates that the highest percentages of reactions occurred on days 1 and 2. Crying occurred predominantly on day 1. On day 3 minor reactions occurred only in low percentages. For example, fever occurred on that day after 3·2% of inoculations. Inconsolable crying for more than three hours occurred on day 3 only in four cases. A red area (>2 cm) occurred on day 3 after 2·8% of inoculations, swelling after 10·1%, pain after 3·8%.

In some cases reactions persisted until after day 3. In 2·7% of all cases the reaction was fever. In nearly all these cases fever had disappeared within five days of inoculation. After 6·0% of inoculations there was a local reaction which persisted until after day 3. Half of these reactions had disappeared within five days. If not, there was generally a solid lump or



Minor symptoms on the day before DTPP vaccination (day 0), the day of the vaccination (day 1), and the two days after (day 2 and 3); data from 2026 vaccinations.

a haematoma. After 2·4% of inoculations, general symptoms persisted until after day 3.

Day before vaccination

Minor symptoms can also occur without inoculation. In order to get an impression of the frequency of these symptoms on a 'normal' day the parents filled in the questionnaire on the day preceding inoculation (day 0). It should be noted that day 0 is not a completely arbitrary day. Given the fact that on the next day there were no contraindications to inoculation, the children were probably slightly healthier than on a completely arbitrary day.

In the figure percentages are given per day for all minor symptoms, starting from the day before inoculation. On day 0 all types of general symptoms occurred. However, on the day of inoculation (day 1) these 'reactions' occurred

Table 2 Summary of minor reactions after the fourth DTPP vaccination, per site of injection, in percentages

Minor reactions	*Arm (n=213)*	*Leg (n=247)*	*p Value**
Temperature			
<38·0°C	18·8	25.1	0·1†
38·0–38·9°C	64·8	61·5	
≥39·0°C	16·4	13·3	
Local			
Redness >2 cm	46·5	15·8	<0·0001
Swelling	49·8	41·3	0·07
Pain	76·5	70·9	0·17
Combination	30·0	13·8	<0·0001
Crying			
Increased	72·3	72·9	0·9
Inconsolable			
1–3 hours	8·9	6·5	>0·5†
≥3 hours	2·3	2·4	
Other general symptoms			
Sleeping changes	66·2	64·4	0·7
Eating changes	46·0	47·0	0·8
Vomiting	6·1	7·7	0·5
Drowsiness	42·3	44·9	0·6
Fretfulness	56·3	53·0	0·5
Combination	3·3	3·2	0·98

*χ^2 test for 2×2 table, with exception of †.
†χ^2 test for linear trend, 1 df.

more frequently: fever 20 times more often, crying 10 times more often, other general symptoms twice to 15 times more often. On day 2 percentages of minor reactions were of the same order as on day 1. Figures show that most symptoms that occurred after a DTPP vaccination must be considered as reactions to the inoculation.

INFLUENCE OF SITE OF INJECTION

Vaccinations were given in the arm, upper leg, or buttock in 12·9%, 85·7%, and 1·3% of all inoculations respectively.

If the inoculation was given in the arm, it was in nearly all cases the fourth one. The fourth inoculation was give 213 times in the arm and 247 times in the leg. Our analysis includes data on whether the choice of the injection site at the fourth inoculation has an influence on the frequency of minor reactions.

Table 2 shows that after inoculation in the arm, redness occurs significantly more frequently than after inoculation in the leg. Also, fever and inconsolable crying occurred more frequently after inoculation in the arm, but these differences were not significant. No difference was observed in other general symptoms after arm and leg inoculations.

INFLUENCE OF SEX

There were 282 boys in the study, for whom 1061 forms were returned, and 258 girls for whom 965 forms were returned. There appeared to be no difference in the occurrence of minor reactions between boys and girls.

ASSOCIATIONS BETWEEN MINOR REACTIONS

The four categories of minor reactions were examined for associations. An association between two different symptoms was considered likely when they occurred more frequently after the same injection than might have been expected on the basis of chance. The association was analysed for each of the four inoculations separately, so that analyses were based on independent observations each time. Associations were considered only if they were assessed for each of the four vaccinations.

Fever seldom occurred as an isolated symptom; it showed a significant association with (i) one or more local reactions, (ii) with increased crying, and (iii) with two or more of the five general symptoms. Of the association between fever and local reactions, only the association between fever and pain at each of the four vaccinations was significant ($p<0·01$). In contrast to increased crying, no association existed between inconsolable crying for an hour or more and fever. Pain and increased crying were strongly related; this applied also to the subgroup of inconsolable crying for at least one hour.

RISK OF RECURRENCE

Chances of fever, redness, and crying after DTPP vaccination increased if these symptoms occurred after preceding inoculation(s). Depending on the series number, chances increased roughly by a factor 1·5 to 3. With high fever (≥39·0°C), severe redness (>8 cm), and inconsolable crying for more than one hour, chances of recurrence increased most, by a factor of approximately five.

Discussion

All recorded general symptoms occurred in varying frequency on the day before inoculation. This study shows, however, that the great majority of symptoms that occur after DTPP vaccination must, indeed, be considered as *reactions* to that inoculation.

Minor reactions occurred frequently. In this study only 4% of all vaccinations were not followed by a reaction within 48 hours. Fever (≥38·0°C) occurred after 68% of inoculations, local reactions after 66%, increased crying after 64%, and other general symptoms (including changes in sleeping and eating patterns, and fretfulness) after 80%.

Serious symptoms occurred rarely. After 2026 vaccinations no collapse, convulsion, or other neurological complications occurred. A temperature of ≥40·0°C occurred 12 times (0·6%), in three cases ≥40·5°C. It should be noted, however, that the definitions of serious and non-serious symptoms are still a matter of discussion. This applies particularly to fever and crying. In the USA a temperature of >40·5°C or persistent screaming for more than three hours was until recently a contraindication to further inoculation with pertussis vaccine.[4] In the Netherlands these reactions are not considered as contraindications.[5] In four children with, in total, six changed inoculations, however, the normal vaccination programme was changed as a result of a strong reaction to a previous DTPP. Three children continued to be vaccinated with DTPolio after a strong local reaction (in one child) or high fever ≥40·0°C (in two). One child was vaccinated several times with half a dose of DTPP after a strong crying reaction after DTPP1.

In the literature we find a considerable variation in the reported incidence of reactions after DTP(P) vaccinations. Factors relevant to the interpretation of the data include the composition of the vaccine (in the Netherlands there is only one combined vaccine against diphtheria, tetanus, pertussis, and poliomyelitis), vaccination schedules and ages, series number, definitions of possible reactions, and the manner and frequency of observation.

In our study, a large number of children reacted with fever. In the only other Dutch study, approximately 23% of children experienced a temperature of ≥37·5°C. It should be noted, however, that in that study there were no fixed times of measurement.[6] In other studies, the percentage of children with a fever of ≥38°C varies between 46·5%[2] and 66%.[7] The percentage of subjects with high fever is also high in our study: 9·9% at ≥39·0°C. In other studies, the figure varies between 3% at ≥39·4°C[7], 4·2% at >38·9°C,[3] and 6·1% at >39·0°C.[2] Differences in the definition of high fever complicate the comparison of these figures and may partly explain variations.

In our study, paracetamol or aspirin was administered to the child after 11% of vaccinations. These drugs can influence temperature, pain, and associated behavioural reactions. Half of the cases were related to the fourth vaccination. Generally, drugs were administered only after occurrence of a reaction and not prophylactically. Other studies report much higher percentages of drug intake after inoculation. Barkin (Denver, USA) mentions the use of drugs in 65% of cases[3] and Long (New York, USA) in 75% of cases.[7] The less frequent use of antipyretics in our study may partly explain the rather high frequency of fever recorded.

As to local reactions, there are no notable differences between our results and those from others. Cody *et al* found local reactions after 64% of vaccinations,[2] Barkin and Pichichero after 72%,[3] and Swaak after 63%.[6] Only Long *et al* found a much higher incidence (85%).[7]

DTPP4 inoculations were given both in the arm and the leg; thus it was possible to compare the two injection sites. A remarkable difference was found. Redness, fever, and inconsolable crying for more than an hour occurred more frequently after inoculation in the arm; the difference in redness was significant. It is, therefore, worth considering administering DTPP4 in the leg.

Frequency of local reactions was different between sequential inoculations. After the fourth inoculation local reactions occurred more frequently than after the three preceding inoculations. The difference in redness, however, was caused by the fact that DTPP4 was often given in the arm. There was very little difference in the occurrence of redness between the fourth and the preceding inoculations in children who were vaccinated exclusively in the leg.

Baraff *et al* studied the effect of the injection site for DTPertussis 1, 2, and 3 (primary vaccinations) and compared the anterior midthigh, the upper lateral thigh, and the buttock.[8] Local swelling, pain, and fever occurred less frequently after immunisation in the buttock than in the thigh. Persistent crying, however, occurred more frequently after inoculation in the buttock. None of the three injection sites, however, were associated with an overall lower frequency of reactions. Baraff assumed, therefore, that general reactions are not related to the degree of local reaction. In our study, however, an association was found between fever and pain after each of the four inoculations.

In this study, reactions occurred more frequently after DTPP4 (administered at the age of 11 months in the Netherlands), than after any of the three preceding inoculations. This was found in other studies also.[2 3 6 7] In our study, these differences were most noticeable for fever and local reactions (table 1). In this regard it may be noted that paracetamol/aspirin was administered more frequently after DTPP4 than after DTPP1, 2, or 3. Inconsolable crying showed a different pattern: this reaction decreased after repeated inoculations.

In a study of 772 children the incidences of fever ≥39·0°C, continuous crying for more than half an hour, and a red area exceeding 2·5 cm were compared with the same reactions after the previous inoculation.[8] The incidence of these reactions was two to three times higher in children who had experienced a similar reaction after the preceding inoculation; but these differences were not significant except for redness. In our study, the occurrence of high fever (≥39·0°C), severe redness (>8 cm), and inconsolable crying for one hour or more increased significantly, approximately by a factor of five, in children with the same symptoms after preceding inoculation(s).

As this study shows that symptoms occur very frequently after DTPP vaccinations, we strongly suggest that the parents of the vaccinees be well informed about the nature, frequency, and risk of recurrence of these predominantly non-serious reactions.

In assessing the importance of minor reactions, they should be measured against the great benefits of these vaccinations. However, because minor reactions occur frequently and tend to cause discomfort, they (as well as major reactions) should be included in the assessment of new DTPP vaccine formulations.

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Enhanced thrombin generation in patients receiving intensive care

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Abstract

Thrombin–antithrombin III complex (TAT) concentration was measured in 27 control and 155 intensive care patients to (a) establish normal reference ranges, (b) measure thrombin generation in critically ill patients, and (c) determine the characteristics of the TAT assay for the diagnosis of disseminated intravascular coagulation (DIC) in children.

The normal reference range was 1–4·3 μg/l (median 2·3 μg/l), and 89·7% of patients had raised TAT concentrations. Median TAT concentrations in the presence of DIC (27 μg/l) were significantly higher than in its absence (8 μg/l). Sensitivity, specificity, and positive and negative predictive values of the assay were 97·3%, 28·3%, 76·3%, and 81·3%, respectively, at a cut off of 4 μg/l.

Excess thrombin production occurs in the majority of critically ill children. The TAT assay is potentially useful in the diagnosis of DIC in children.

Disseminated intravascular coagulation (DIC) occurs as an epiphenomenon in many disorders which necessitate admission to the intensive care unit, such as infections, massive tissue trauma, malignancy, postoperative states, vasculitis, and severe acute haemolysis[1]; and it is frequently fatal.[2 3] DIC is initiated by excessive thrombin generation and is characterised by fibrin deposition in the microvasculature, consumption of haemostatic factors, and activation of fibrinolysis.

Current diagnostic tests for DIC are insensitive and non-specific,[4] and measurement of in vivo thrombin generation and/or fibrinolysis may be more useful. D-dimers (the D fragments of fibrinogen) are more specific markers for DIC than are fibrin degradation products[5] but are indirect measures of hypercoagulability. Thrombin is inactivated in vivo by antithrombin III to form an inactive complex, thrombin–antithrombin III complex (TAT). Measurement of TAT may give an earlier and more direct indication of a prethrombotic state. TAT concentrations have been measured in DIC and other prethrombotic states in adults[1 2 6–14] but there are only anecdotal reports in children.

The purpose of this study was to (a) establish normal reference ranges for TAT in children, (b) measure thrombin generation in a group of children at high risk of DIC, and (c) determine the characteristics of the TAT assay for the diagnosis of DIC.

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Patients and methods

PATIENTS

A prospective study was made of 155 children admitted consecutively to our intensive care unit, and 27 healthy children having elective minor surgery (for example, circumcision) acted as controls. In the first 19 patients paired samples were collected to test the variations in TAT concentrations with two commonly used anticoagulants. The study was approved by the hospital ethics committee.

BLOOD COLLECTION

Samples were collected by direct venepuncture as soon as possible after admission before the administration of blood or blood products. Blood was collected in standard 2 ml coagulation tubes (Teklab) containing 0·11 M trisodium citrate (nine parts blood to one part citrate). For paired samples, additional 2 ml bottles (Sarstedt) containing solid dipotassium EDTA (1·6 mg/ml of blood) were used.

SAMPLE PREPARATION

Samples were centrifuged within one hour of collection at 3000 rpm (1200–1500 *g*) for 15 minutes. Two 300 μl aliquots of plasma were separated into 2 ml polypropylene cryopreservation tubes and frozen initially at −20°C. Within six hours both 300 μl aliquots were transferred to −70°C. One 50 μl aliquot was frozen at −20°C. D-dimers were run in batches within 24 hours using the frozen 50 μl aliquot. TAT assays were performed on specimens stored at −70°C. Coagulation screens were performed within two hours of sample collection.

ASSAYS

TAT

The commercially available kit (Enzygnost-TAT, Behringwerke AG, Marburg, Germany) was used. The test is an enzyme immunoassay based on the sandwich principle. The normal reference range for adults is 1–4·1 μg/l.

D-dimers

Agen Dimertest Latex Kit (Agen Biomedical Ltd) was used. The test is a slide agglutination test using polystyrene latex beads coated with D-dimer antibody and 10 μl of plasma. A positive test is indicated by agglutination at 3 minutes.

Other assays

Microassays for prothrombin time, activated partial thromboplastin time, thrombin clotting time, and fibrinogen were carried out on all samples using the methods described by

Johnston and Zipursky.[15] Platelet counts were measured using a Sysmex M2000 cell counter.

CRITERIA FOR DIC

DIC was diagnosed if at least two of the following were present: prothrombin time >20 s, activated partial thromboplastin time >50 s, fibrinogen <1·5 g/l, platelets $<150\times10^9$/l or D-dimers >0·2 mg/l.

STATISTICAL METHODS

Inter group variations in TAT were compared using one way analyses of variance (ANOVA) followed by multiple range analysis (Scheffe's test). Continuous variables were compared using the Mann–Whitney U test. Spearman's rank correlation was used to test the relationship between TAT and concurrently assayed coagulation parameters. Sensitivity, specificity, positive predictive value, and negative predictive value were calculated at different cut off values of TAT. The level of statistical significance was taken as p<0·05.

Results

EFFECTS OF DIFFERENT ANTICOAGULANTS ON TAT CONCENTRATIONS

No significant differences in TAT concentrations were seen in the 19 paired samples collected into trisodium citrate or dipotassium EDTA (difference between medians=0·2, p=0·31). Hence in all other patients only citrated samples were collected.

CONTROLS

The 27 control children had a median age of 18 months (range 3 days to 12 years). All had normal coagulation by standard assays (that is, prothrombin time <18 s, activated partial thromboplastin time <48 s, thrombin clotting time <13 s, fibrinogen >1·5 g/l and D-dimers <0·2 mg/l) and normal platelet counts. The median TAT concentration in these children was 2·3 µg/l (range 1–4·3 µg/l) and they showed no age or sex related differences.

PATIENTS

The median age of the 155 patients (96 male, 59 female) was 21 months (range 3 days to 18·6 years). There were 85 admitted postoperatively and 70 had a variety of disorders.

Overall, 139 out of 155 patients (89·7%) had raised TAT concentrations (>4·3 µg/l). Median TAT concentrations were above normal in all major diagnostic categories of patients without significant variations in relation to diagnosis (table 1).

TAT CONCENTRATIONS IN DIC

DIC was diagnosed in 110 (71%) patients using the criteria described above. Of these, 14 patients had fulminant DIC manifested by frank bleeding, multiorgan failure, and grossly deranged coagulation. The remaining 96 patients had low grade DIC (36 with laboratory but no clinical evidence of DIC, and 60 with minor bruising only). The median TAT concentration in DIC was 27 µg/l (range 3·8–70 µg/l). In 45 (29%) patients there was no clinical evidence or laboratory evidence of DIC. The median TAT concentration in these patients was 8 µg/l (range 1·8–70 µg/l). TAT concentrations in the presence of DIC were thus considerably higher than in its absence (p<0·0001). The values obtained in both groups of patients were significantly higher than in controls (p<0·001). There was a correlation between maximum TAT concentrations and severity of DIC. The highest concentrations were recorded in fulminant DIC. Concentrations of >60 µg/l (the upper limit of detection in undiluted plasma) were recorded in 50% of patients with fulminant DIC and 18·7% of patients with low grade DIC, but only 4·3% of patients without DIC. There was no correlation between TAT concentrations and outcome. The sensitivity, specificity, and the positive and negative predictive values of the TAT assay for the diagnosis of DIC at different cut offs is shown in table 2. At a cut off of 4 µg/l (95th centile of the control group) the values were: 97·3%, 28·3%, 76·3%, and 81·3% respectively. At higher cut offs there is an improvement in specificity and positive predictive value but a fall in the sensitivity and negative predictive value, most noticeable above a cut off of 10 µg/l.

Table 1 Incidence of DIC and TAT concentrations in different diagnostic groups

Diagnostic group	No	DIC	TAT (µg/l)	
			Median	Range
Postoperative	85	64	21	3·4–60
Septicaemia	17	17	23	3·2–66
Viral infections	13	2	12·4	1·8–70
Bacterial infections (without septicaemia)	10	6	11·3	3·8–70
Malignancy	5	5	21	3·4–70
Trauma	4	4	20·5	12–70
Miscellaneous	21	12	18·4	2·3–60
Controls	27	0	2·3	1–4·3

CORRELATION OF TAT WITH OTHER COAGULATION PARAMETERS

There was a moderately significant positive correlation between TAT and concurrently assayed prothrombin time (r=0·51, p<0·001) and activated partial thromboplastin time (r=0·42, p<0·001), a weak but significant correlation with D-dimers (r=0·24, p=0·002), and a moderately significant negative correlation with fibrinogen (r=−0·41, p<0·001) and platelets (r=−0·32, p<0·001).

Discussion

Thrombin generation represents a pivotal event in coagulation. Thrombin cleaves fibrinopeptide A and B from fibrinogen, leaving soluble fibrin monomer which polymerises rapidly to form the

Table 2 Characteristics of the TAT assay for the diagnosis of DIC

TAT (µg/l)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
4	97·3	28·3	76·3	81·3
5	94·5	34·7	77·4	72·7
10	83·5	58·7	82·7	60
20	56	71·7	82·4	40·7
40	38·5	86·9	87·5	37·4
60	23	95·6	92·6	34·4

fibrin clot. It also activates factor XIII which catalyses the formation of stable fibrin polymer.[16] Antithrombin III inhibits thrombin (to form TAT) as well as factors IXa, Xa, XIa, and XIIa and thus modulates the activity of the coagulation system.[17–20]

TAT concentrations seemed to be uninfluenced by the choice of anticoagulant. After obtaining the results on the first 19 patients, it was deemed necessary to use only citrated samples. This gave us the advantage of obtaining a coagulation screen and TAT value on a single 2 ml sample of blood.

Low grade generation of thrombin is a normal phenomenon in children and we were able to establish a normal reference range of 1–4·3 μg/l. This is very similar to the normal adult reference range quoted by the manufacturers although concentrations of 0·85–3·2 μg/l and 2·1–9·9 μg/l have been recorded by Pelzer *et al*[7]and Boisclair *et al*,[21] respectively, in healthy adults.

Excessive thrombin generation was present in as many as 90% of critically ill children with a variety of underlying disorders, indicating an underlying prethrombotic state. The sample of children in this study was representative of the population admitted annually to our paediatric intensive care unit and included two groups (viral infections and bacterial infections without septicaemia) not previously shown to be associated with raised TAT concentrations. The action of thromboplastins generated by trauma, shock, hypoxia, burns, or sepsis potentiates this prethrombotic state, and together with the reticuloendothelial blockade which is common in critically ill children makes the triggering of DIC particularly likely.[22] This was confirmed by the high incidence (71%) of DIC in these children.

As expected, median TAT concentrations were significantly higher in the presence of DIC than in its absence, all but three of the 110 children (97·3%) with DIC in our study having raised TAT concentrations. The incidence of raised TAT concentrations in adults with DIC has been variably reported between 61% and 97%.[2 6 21]

The sensitivity of TAT for the diagnosis of DIC has ranged from 80% to 96·7% and the specificity from 39% to 63% in adult studies,[2 6] explained in part by the different diagnostic criteria used for defining DIC and different cut offs of TAT employed. We selected our criteria to include cases of low grade DIC. Using our criteria, the specificity of the assay at a cut off of 4 μg/l was low (28·3%), although the sensitivity was high (97·3%). Because critically ill children produce excess thrombin even when DIC is not present, a higher cut off (10 μg/l) may be more appropriate in children. At this level, even though there is some loss of sensitivity, the specificity and the positive predictive value (which indicates the degree of confidence in the diagnosis based on a positive assay result) are considerably improved.

The correlation of TAT with other coagulation parameters reflects the high incidence of DIC in our patients, but we found a much weaker correlation with D-dimers than previously reported in adult studies,[21] either because complete neutralisation of thrombin by antithrombin III had taken place or fibrinolysis, being a later event had not yet occurred. Our study was confined to single samples taken soon after admission. This may not be optimal, and some cases of developing DIC may have been missed. Estimating TAT on serial samples may be more useful both in detecting these cases and in monitoring the efficacy of treatment of DIC; TAT concentrations would be expected to fall as clinical improvement took place.

Our study confirms that as in adults, the TAT assay is potentially useful in the diagnosis of DIC in children. Its role in monitoring the treatment of DIC needs to be further evaluated.

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Troublesome crying in infants: effect of advice to reduce stimulation

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Abstract

The observation that babies with troublesome crying improve quickly in hospital suggested that, if true, a common, quickly reversible, factor may operate. Histories from parents of such babies suggest that much work goes into trying to console them. It is hypothesised that this may lead to excessive stimulation and the improvement seen in hospital reflects a reduction in stimulation.

Two studies were undertaken. (1) Carers were asked to agree to randomisation of their infants to hospital or home management. Those at home were advised to reduce stimulation. A 10 point questionnaire was used to describe distress in mothers of subjects and age matched controls. (2) A randomised controlled study compared advice to reduce stimulation with an empathic interview using a $+5$ to -5 scale to chart change. In the first study too few subjects agreed to randomisation and thus a rigorous study to validate the observation could not proceed. There was good evidence, however, that crying improved. Results from the home group justified the second study. The median distress score for subjects was 7/10 and for controls 3/10 ($p<0{\cdot}001$). In the second study at seven days, 18/22 subjects given advice scored $+2$ or better on the change chart for crying, compared with 7/20 of those who did not receive advice ($p<0{\cdot}01$). After the latter received advice 79% improved (95% confidence interval 61 to 97%). For babies under 12 weeks, the customary upper limit for a diagnosis of colic, 14/15 subjects advised improved compared with 6/12 who were not advised ($p<0{\cdot}02$).

These studies have shown that infants with troublesome crying admitted to hospital seem to improve quickly as do those whose carers are advised to reduce stimulation.

There are two broad proposals to explain the problem of troublesome crying in infants.[1,2] One proposal suggests an organic cause for a syndrome of excessive crying in infants of less than 3 months of age that is presumed to be caused by pain and excessive flatus, that is, colic. The second suggests a non-organic, developmental, or behavioural cause.

Because of the uncertainty of the cause there have been, understandably, large numbers of proposed treatments and interventions. Although 20 years ago Brazelton urged mothers of babies with troublesome crying to 'offer lactose (at least hourly) to facilitate mobilisation of stomach gas',[3] lactose intolerance is nowadays the front runner in the organic category of proposed causes of troublesome crying. There is no evidence to date, however, that either milk allergy or lactose intolerance is responsible for excessive crying. Taubman demonstrated in a group of symptomatic babies that a reintroduction of cows' milk after its elimination did not reproduce symptoms.[4] It has yet to be shown in babies with colic that an increase in breath hydrogen excretion, suggestive of lactose intolerance, is not a secondary phenomenon.[5,6] Hunziker and Barr have suggested that increased carrying is helpful in reducing crying in normal babies less than 3 months old and may prevent infant colic.[7] Others suggest that a reduction in picking up[8] or systematic ignoring[9] are also helpful. Taubman concluded from a successful study of counselling parents about how to respond to infant crying that a major cause of colic was the misinterpretation of infant cries leading to ineffective responses.[10]

Background and observations

In 1986 a crying baby referral system was organised in Romford. Babies referred had no clinical features to suggest that any organic disorder was the cause of the principle symptom, inconsolable crying, which was causing considerable distress to carers. Some babies were admitted to hospital, mainly because it was felt that a carer might harm the child.

Most of the hospitalised babies' crying improved within a day or two. This suggested that there might be a common factor operating in hospital that was not operating at home. If that was identified then it might be possible to treat babies at home; it might also be possible to gain some insight into the cause of troublesome crying.

Also noticeable, both on history and on observation, was how hard the carers worked to try to stop the crying. Was it possible that this resulted in too much stimulation and that such infants' crying would be less troublesome in hospital because the nurses were not intervening in the same way?

Purpose

Two studies were undertaken:

STUDY 1

(a) To record biographical details and distress of carers attending the clinic.

(b) To discover if carers were willing to enter a randomised study of home versus hospital treatment to validate the observation that when babies with troublesome crying are admitted to hospital there is a clinically important reduction in crying.

(c) To examine the use of change rating charts.

(d) To discover whether the effect of advice to reduce stimulation at home was sufficient to justify a second study.

STUDY 2

To discover if advice to reduce stimulation of babies with troublesome crying managed at home was more effective than an empathic interview only.

Methods for both studies

Troublesome crying was defined as crying with which parents felt they could no longer cope and for which they sought help. Babies <1 year old were referred by health visitors and general practitioners. Consecutive babies were enrolled for both studies. Families were interviewed within 72 hours of referral in an office separate from outpatients. Only the interviewer and the family were present. This setting was designed to facilitate trust between the carers and paediatrician. General practitioners or community doctors had already assessed the baby to exclude physical illness.

Biographical data

The age at time of referral, position in family, length of time of troublesome crying, the pattern and length of crying or 'whingeing' (the local term for fussing) in the previous 48 hours, the carers' perception of the problem and the interventions already tried, and obstetric, feeding, family and social histories were recorded. The purpose of gathering this information was not only to describe the patient base but also to facilitate an empathic relationship between interviewer and carer(s).

Distress score questionnaires

Each mother (fathers did not always attend) was asked to answer a 10 point 'distress score' questionnaire (table 1). Five subgroups of items highlighted poor self esteem (items 1–3), feelings about the baby's manipulation (items 4, 5), anger (items 6, 7), effect on health (items 8, 9), and other relationships (item 10). The questions had been understood by previous families in a pilot study.

Table 1 Distress questionnaire

Since the birth of your baby have you ever felt:

(1) Not a good mother	Yes/no
(2) Helpless	Yes/no
(3) Cannot satisfy baby	Yes/no
(4) Baby crafty/sly	Yes/no
(5) Baby deliberately preventing you from having anything for yourself	Yes/no
(6) Feel like hitting/getting rid of baby	Yes/no
(7) Other feelings of anger	Yes/no
(8) Exhausted/frustrated	Yes/no
(9) Sleeping/eating badly	Yes/no
(10) Quarrelsome	Yes/no

Advice to reduce stimulation

The carers were asked not to pat, wind, or lift their babies excessively. They were also asked to cuddle the baby gently, to distinguish between rocking (a relaxed 60 beat per minute swaying movement of baby in arms or on chest) and jiggling (a >140 beat per minute jerking movement of baby on knees or in arms) and to avoid the latter. They were also to reduce stimulation from loud music, rattling toys, etc, and not to intervene during the early part of a sleep when the baby may vocalise and appear restless—an explanation of active sleep was given. An assurance was given that a certain amount of crying is normal and may occur at the beginning of sleep. Finally, the carers were given permission to leave their infants if they felt that because of the crying they could no longer tolerate their being close.

Change rating charts

A change rating chart was used to record the change in both the crying and in the mothers' distress on day 3 and day 7. This chart was simply a line divided into equal intervals from +5 (better) through 0 (no change) to −5 (worse). Carers were asked to indicate on the chart a score which best reflected change in both crying and distress from the time of the first interview. A score of +2 or better or −2 or worse was considered a clinically important change.

STUDY 1

Thirty one subjects were enrolled and 31 age matched controls were randomly selected from well baby clinics. The median age was 10 weeks (range 3 weeks—10 months) and for the subjects the median length of crying was 8 weeks (range 1 week–8 months) before the first interview. There was no difference between subjects and controls either in the position in the family or in the type of feed offered. The median number of hours crying or whingeing during the 24 hour period before the interview was 12 hours (4–21) for the subjects and less than 3 hours (0–12) for controls. Two of the controls admitted to troublesome crying.

Total distress scores for each patient (out of a possible total of 10) were calculated from the distress questionnaires and scores for subjects and controls were compared by Wilcoxon rank sum test for paired values. As the subgroups of selected items were of unequal size, an alternative score was calculated in which one or more positive responses in a subgroup scored 1, giving a maximum score of 5, but the results were very similar and will not be reported.

The median score for subjects was 7 (range 3–10) and for controls was 3 (range 0–3) ($p<0\cdot0001$). The median difference within patient-control pairs was +3 (range +7 to −3) ($p<0\cdot0001$).

Subjects were asked to agree to randomisation or to elect for their babies to be managed either in hospital or at home. Those at home were asked to reduce stimulation of their babies and to keep diaries of crying times. Those in hospital stayed for three days. Only one mother of 13 hospitalised babies stayed with her baby. As expected too few parents agreed to randomisation and so a formal comparison of hospital and home management could not proceed. The babies in hospital did however cry much less (2·5 hours/day compared with a reported 12 hours before admission) and this was concordant with the improvement in the change rating scores. This improvement was sustained after discharge.

Half of those managed at home did not return diaries or returned diaries which they admitted were incomplete. Those managed at home also improved significantly.

This study showed that a randomised comparison between hospital and home care would be impractical, as was the use by home carers of detailed crying diaries. However, it was established that a combination of interview and advice to reduce stimulation suggested a substantial improvement in babies managed at home. The second study was undertaken to examine the part played by the giving of advice.

STUDY 2

This examined whether advice to reduce stimulation helped more than just an empathic interview.

Methods

In the first study, 80% of babies with troublesome crying managed at home achieved change scores of +2 or more at day 7. It was considered that a difference of 40% in this proportion between an advice and an interview only group would be of practical importance. To demonstrate this with a type 1 error of 0·01 and a type 2 error of 0·2, it was planned to enrol 30 babies in each arm of a randomised trial. It was also planned to make a single interim analysis when 20 babies had been enrolled in each arm. As before, a change score of +2 or better was counted as a positive response, and the proportions of such responses were compared using χ^2 testing with Yates's correction for continuity.

Carers were interviewed as in the first study. All carers were given an optimistic outlook. All agreed that information about their babies' crying and its management could be used in a research project. It was considered ethically acceptable that families should not be asked to agree to randomisation as knowledge of this may have prejudiced the quality of the information gathered; all eventually received the same treatment. Patients were randomised into two groups using random numbers. Each subject of the 'empathy' group was asked to fill in a diary of crying times and interventions for a week. This diary record was not for formal analysis; it was explained to the families that it would provide a background for advice in seven days time. The other group was advised to reduce stimulation. All were given a change rating chart and knew they would be contacted by telephone by someone who was not involved in the study and who would therefore not be able to advise.

All were contacted by telephone on days 3, 7, 10, 14, and at one month by an observer, usually a house officer, who did not know to which group infants had been assigned. The observer was given written instructions about how to conduct the telephone conversation with examples of questions and responses; he was asked to introduce himself by first name only and to request the results of the change scores on that day. Observers were to avoid conversation about anything else. All carers were contacted on the same days by the interviewer who did not know the results of the change scores. 'Empathy' group subjects returned on the afternoon of day 7 and were given the same advice about reducing stimulation as the other group.

Results

When 45 infants were enrolled an interim analysis was made. Three babies were not included: one requested hospital admission and two were not available on the telephone. The median age was 10 weeks and the median distress score was 7 (4–10).

The results of the change scores for crying on day 7 are shown in fig 1 and all results are summarised in table 2. Three families were not available after seven days for follow up. The proportion of positive responses, both for babies' crying and for mothers' distress, was significantly higher in the 'advice' group on days 3 and 7. At this point the empathy group also received advice, and the proportion of

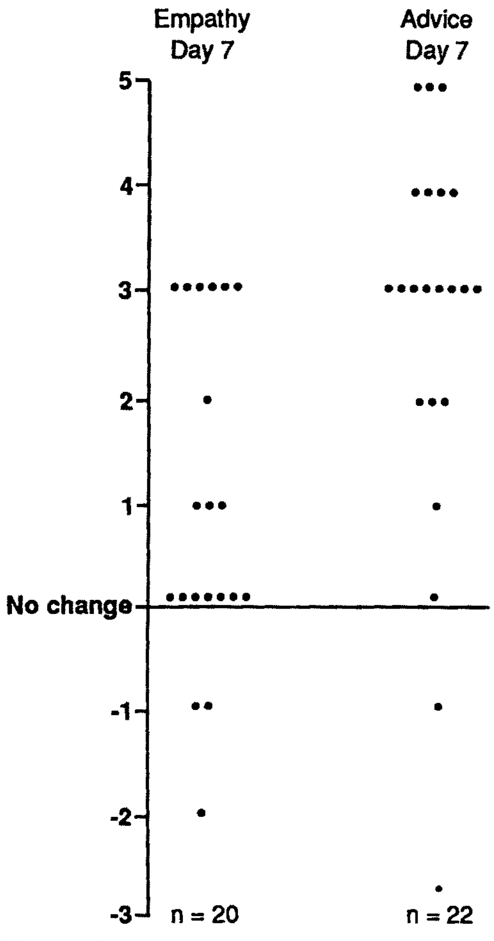

Figure 1 Change in crying seven days after start of study.

positive responses rose to a level similar to that in the 'advice' group (fig 2). The results appeared sufficiently clear cut that no further subjects were enrolled. Thirty nine families were available for follow up one month after receiving advice and their change scores showed 36/39 mothers scored +2 or better (22=+5) and 30/39 babies scored +2 or better (19=+5).

Athough it was not the original intention to enrol enough babies for an analysis of separate subgroups, the opportunity was taken to examine the outcome for those aged below 12 weeks. This is the age many believe is the upper limit for colic. Twenty one of 27 carers with babies 12 weeks old or less offered a cause of the crying as colic or wind compared with nine of 15 with older babies (χ^2=0·22; p=>0·5). Items 4 and 5 of the questionnaire—perception of baby's wilfulness—were examined in babies older and younger than 12 weeks. The younger babies scored 23 out of a possible total score of 54 compared with a score of 9 out of a possible 30 for older babies (χ^2=0·82; p=>0·1). In babies less than 12 weeks six of 12 babies in the empathy group score +2 or better after seven days compared with 14 or 15 in the advice group (χ^2=4·4; p<0·02).

Table 2 'Empathy' and advice management. Numbers of babies and mothers who scored +2 or better on the change rating charts for baby's crying and mother's distress. The empathy group received advice on day 7

	Empathy (%)	*Advice (%)*	*p Value*
Crying:			
Day 3	4/20 (20)	14/22 (64)	<0·02
Day 7	7/20 (35)	18/22 (82)	<0·01
Day 10	13/19 (68)	15/20 (75)	>0·5
Day 14	16/19 (84)	16/20 (80)	>0·5
Mother's distress:			
Day 3	4/20 (20)	15/22 (68)	<0·01
Day 7	6/20 (30)	19/22 (86)	<0·001
Day 10	14/19 (74)	17/20 (85)	>0·5
Day 14	16/19 (84)	16/20 (82)	>0·5

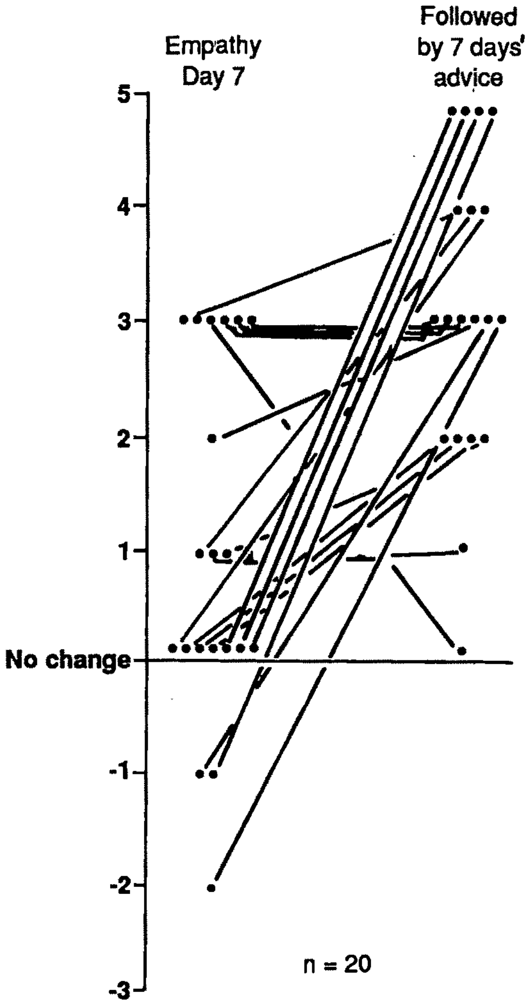

Figure 2 Change in crying in 'empathy' group after a further seven days advice; 79% (95% confidence interval 61 to 97%) improved.

Discussion

Implicit in the term 'troublesome crying' is the distress a baby's crying causes carers. In any study of this problem some measure of carers' distress should be made so that comparisons with future studies are possible. The 10 point distress score used in this study separated subjects and controls with very little overlap. It may well be that the completing of the questionnaire has a value of its own as it validates carers' feelings.

The observation that some babies with troublesome crying improve after hospital admission has been made before.[11] In the present study, as expected, too few carers agreed to randomisation for home or hospital management to encourage the undertaking of a rigorous study to validate properly the observation. Nevertheless, the results indicated that babies nursed in hospital improved quickly and this was sustained after discharge.

The results of the second study which compared the effect of an empathic interview with such an interview augmented by specific advice to reduce stimulation indicate that advice is helpful. Whether this is any better than any other advice or intervention is not known. There is of course no evidence that stimulation was reduced. The effect of the empathic interview alone cannot be measured from this study as no group was identified who would be followed up in the community. Such a study was beyond the scope of this project.

The findings of both studies do not support the hypothesis that most troublesome crying is due to a primary organic cause. As lactose intolerance appears to be an important candidate for such an organic cause it would be interesting to undertake hydrogen breath studies in a group of babies with troublesome crying admitted to hospital under conditions similar to this study. If the crying stops quickly without a change in diet a return of breath hydrogen to normal would suggest that previous raised levels are secondary, perhaps due to increased gut motility.[12] This might result from sympathetic stimulation caused by the effort and exercise of excessive crying.

The diagnosis within the community of '3-month colic' is based on the observation that crying with wind improves at this age. Levine describes changes in caretaking practices in infancy which move from emphasising survival to the transmission and maintenance of cultural values and goals.[13] It is possible that around 3 months, carers respond to crying differently than they did before this and this may be the reason the crying stops. Indeed, Brazelton advises parents of 3 month old infants not to respond to cries and activity during waking periods and to 'condition' infants to use their own resources for sleep as early as possible.[14] In other words, parents may worry that their baby has an organic cause for the crying in the first few months, may work hard to soothe the crying and to reassure themselves that the baby is healthy, and then make less of an effort once they perceive the baby as healthy and perhaps 'wilful'. In this study carers differed from this model. They were distressed by the crying and, having already seen their own doctor and been reassured that no organic cause could be found, sought help. Both colic and wilfulness were described throughout the age range studied. The advice worked for babies less than 3 months just as well as for those older. Thus the crying may well have a similar root.

At first sight this study's findings may appear contradictory to the findings of Hunziker and Barr who indicated that increased carrying reduced crying.[7] Their study, however, considered babies' 'normal' crying. Pederson has indicated that rocking is helpful in reducing activity but there has been no rigorous examination of the effect of rocking after crying has become troublesome.[15] In this study, parents were asked to hold the babies still or rock slowly in a quiet room. It was explained that some crying is normal[2] and may occur as the baby falls asleep. Many parents reported that they felt that being given the permission to leave the baby if they could not cope was a great step forward. It was not the purpose of this study to examine the cause of troublesome crying but it is tempting to speculate that a carer's excessive jiggling, patting, and winding and other similar manoeuvres in response to crying may be inappropriate. If this is the response to crying at a time when a baby cries or vocalises when falling into active sleep it may prevent progression into quiet sleep and interfere with the development in a very young infant of a normal sleep pattern. Perhaps the encouragement of carrying and very gentle rocking in a peaceful environment in place of more stimulating interventions would prevent troublesome crying in the first place.

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Differences in postperinatal infant deaths between North and Southern Derbyshire

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Abstract

In depth confidential inquiries on all postperinatal infant deaths were carried out for two years in North and Southern Derbyshire District Health Authorities in order to explore why the postperinatal death rates and cot death rates have been consistently higher in Southern than in North Derbyshire.

It was found that the death rates for probably inevitable deaths and for 'idiopathic' cot deaths were the same in both districts. The differences in the death rates lay in the group of partly explained cot deaths. Adverse social factors associated with each death were recorded and an estimate made of their relevance to the individual deaths. The group of deaths most amenable to intervention was those of category B (partly explained cot deaths). As judged by the Jarman index there are more areas of deprivation in Southern than in North Derbyshire.

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Over the past decade the postperinatal infant mortality rates in the Southern Derbyshire Health Authority have exceeded national and regional averages while those in the North Derbyshire Health Authority have remained consistently below the national averages. Two studies failed to explain this finding. First, a working party was set up in 1978 to find out if there were shortfalls in hospital or community services that could have contributed to the high mortality rate within the area. The second investigation involved participation of Southern Derbyshire in the Trent Regional Confidential Enquiry into Infant Mortality during 1984.[1] This inquiry produced information, on individual case inquiry, particularly suggesting the presence of social and service defects but at insufficient depth for action.

Subsequently, analysis of data relating to infant mortality in Southern Derbyshire between 1975 and 1988 was undertaken. A relative rise in children registered as cot death was revealed and the differences between North and Southern Derbyshire were still obvious. In 1987 a system of confidential inquiry into each postperinatal death was incorporated into routine services as part of an ongoing process audit in Southern Derbyshire. North Derbyshire did a parallel study of confidential inquiry to investigate differences in infant mortality between the two health districts under standard conditions over a period of two years, 1987/8. The aims of the study were to compare deaths according to categories of preventability in each health district and to relate each death with home, psychological, and social factors that might have had a major impact on the circumstances leading to death.

Table 1 Categories of preventability by clinicopathological diagnosis

Category	*Diagnosis*
A	Conditions with poor prognosis where deaths are apparently inevitable with the present knowledge and facilities
B	Partially treatable condition present either as a major cause or possible contributing factor to death. Treatable diagnosable conditions under ideal circumstances
C	Death during the course of a minor condition not normally requiring treatment
D	No terminal illness reported. No clinical findings. 'Idiopathic' cot death
E	Accidental death
F	Non-accidental death: (a) Proved non-accidental injury (b) Parental action is a possibly major contributory factor
G	Insufficient information for categorisation into one of the above groups

Methods

The confidential inquiry on all postperinatal deaths involved a study of all casenotes (obstetric, health visitor, hospital, and family doctor), a home visit by a senior health professional, and a conference in the family doctor's office. The inquiry was carried out by persons not directly concerned with the care of any of the families. This method of inquiry was based on the Sheffield model[2] and, to ensure comparability in the study of the districts, a senior clinical medical officer (EA) acted as an independent observer at all case discussions in both districts. Each district had a coordinating doctor.

The questionnaires used were those devised in Sheffield with the addition of a locally devised one for social services inquiry. Postmortem reports were obtained and all of the home interviews were carried out by a senior health professional not concerned with the direct care of the child or family. After collation of all information case conferences were arranged, usually in the general practitioner's surgery. Core members of these conferences were: general practitioner, health visitor, home interviewer, coordinating doctor, and observing doctor. All available information concerning adverse health and social factors in the baby's history was collated, the final classification being made at or immediately after the case discussion. The deaths were classified as in the Sheffield studies (see table 1).[3] Category A deaths are probably inevitable after birth. Category B deaths are those of infants who have disease which, if treated, may have influenced the fatal outcome. Category C deaths are those of infants with minor disease unlikely to have been related to the fatal outcome. Category D deaths are essentially idiopathic with no identified disease on full postmortem examination. Finally category E deaths are accidental, F are probable or proved filicide, and G are those where there is insufficient information for categorisation. A judgment was then made as to the possible preventability or otherwise of the death. At the end of the two year study all notes were reviewed and the A–G classification verified. In each case a listing of all the recorded adverse factors mitigating against the child was made. A further classification was then made as to preventability after birth in the following categories: inevitable, probably inevitable, possibly preventable, probably preventable, and don't know.

Results

During the years under study there were 8802 live births in North and 14 241 in Southern Derbyshire. In North Derbyshire there were 42 postperinatal infant deaths with 18 presenting as cot deaths, and in Southern Derbyshire there were 87 deaths with 47 presenting as cot deaths (see table 2). In Southern Derbyshire there were nine children where there was insufficient information to fully categorise the deaths. In the north there were no such cases. When unexpected home deaths were broken down into their A–G subgroups differences emerged between the two districts (table 2).

The total postperinatal death rate in North Derbyshire was 4·77 compared with that of 6·1/1000 live births in Southern Derbyshire. When the category A deaths (the probably non-preventable deaths) were considered there was very little difference between the districts (2·27 and 2·45/1000 live births). The difference in the total rates was largely due to the lower rate of category B deaths in the North 0·46 compared with 1·3/1000 births in Southern Derbyshire. These differences were further emphasised when the deaths were divided into babies presenting as unexpected home deaths and others, the profiles of the unexpected deaths being clearly different in the two districts while those of the other deaths are very similar.

Table 2 Postperinatal deaths in north and southern Derbyshire 1987 and 1988

	North Derbyshire	*Southern Derbyshire*
Births	8802	14 241
Deaths (rate/1000 live births)	42 (4·77)	87 (6·10)
Cot death (rate/1000 live births)	18 (2·04)	47 (3·30)
Total deaths (rate/1000 live births) by category:		
A	20 (2·27)	35 (2·45)
B	4 (0·46)	19 (1·3)
C	2 (0·23)	9 (0·63)
D	8 (0·9)	6 (0·42)
E	3 (0·34)	1 (0·07)
F	5 (0·57)	8 (0·56)
G	0	9 (0·63)
No (%) unexpected home deaths (cot deaths) by category:		
A	0	1 (2)
B	3 (17)	16 (34)
C	2 (11)	9 (19)
D	8 (44)	6 (13)
E	2 (11)	1 (2)
F	3 (17)	6 (13)
G	0	8 (17)
Total	18 (100)	47 (100)
No (%) other deaths by category:		
A	20 (83)	34 (85)
B	1 (4)	3 (8)
C	0	0
D	0	0
E	1 (4)	0
F	2 (8)	2 (5)
G	0	1 (3)
Total	24 (100)	40 (100)

ADVERSE SOCIAL FACTORS

The factors mitigating against a child were analysed under 34 headings grouped into 12 sections (table 3). These were also related to the clinical groupings on the A–G scale. Medical factors were confined to deaths in categories A and B, these being the only deaths that had had medical involvement. There were six children where there was delay in medical treatment. Non-cooperation with medical services was seen in all groups of death except in group A. Inexperienced parenting predominated in the category F deaths while defective modelling for parenting was evenly distributed among the different categories. Heavy drinking and smoking by parents was associated with category D deaths, which also contained one of the three families that were on drugs. The unsupported mother was the commonest factor identified in the study, occurring in 29 of 129 families but in only one category A death. The history of overdose of a parent was present in one of the category A deaths and five of the other deaths. Depression and possible psychological disturbance was important, the greatest prevalence being in the category F group. Poor housing was common in all categories.

The same applied to family financial problems where debts had accumulated, the commonest being rent arrears and problems with heating bills. These families were not always found in the unemployed category. The number of families out of work in this series was remarkably small. Poor bonding was a joint subjective judgment made by the health visitor, midwife and/or the general practitioner made at the case conference based on their observations of the mother and child during life. This was an assessment of situations where the mother's attitude to the child had been ambivalent or her handling of the child had been inappropriate to that expected. The features emerged only at case conference and had not been recorded on the routine child records. In this group half of the cases came under category F, which was the category that included the only cases where there had been a previous cot death in the family. Social service involvement was prevalent in the category B and F groups. The presence of twins, four baby deaths, appeared to be only associated with the cot death categories of C and D.

The number of adverse factors/case (the adverse factors:case ratio) was worked out for each district and for each category of death (table 4). In group A babies there were 0·29 factors/case compared with an average of 2·7 for all the other categories. In categories B, E, and F the adverse factor case ratio was higher in Southern than in North Derbyshire, the greatest concentration of factors being in categories E and F.

PREVENTABILITY

In the final review of each case an assessment

Table 3 Adverse social factors related to category of death (A–G)

Factor	*A (n=55)*	*B (n=23)*	*C (n=11)*	*D (n=14)*	*E (n=4)*	*F (n=13)*	*G (n=9)*	*Total (n=129)*
Communication defects:								
(1) Hospital to home	3	2						5
(2) General practitioner to hospital	1							1
(3) Hospital to home		1						1
(4) Home to hospital		6						6
(5) Non-cooperation with medical services		2	2	2	1	3	2	12
(6) Very inexperienced parents or low IQ	1	2	1		2	6	2	14
(7) Parents low/defective standard of health		3	3			2	0	8
(8) In care as a child (broken home): mother		2		1	1	2		6
(9) In care as a child (broken home): father				1	1	1		3
(10) Heavy drinker (either parent)			1	4	1	1		7
(11) Heavy smoker (either parent)			2	5		2	1	10
(12) On drugs		1		1			1	3
(13) Single unsupported mother	1	5		1	2	5	1	15
(14) Cohabiting unsupported mother		4	4	3	2		1	14
Mother:								
(15) Depressed/anxious	1	3	2			1	1	8
(16) Personality disturbance		1		2		2		5
(17) Overdose or other method		1		1		2		4
(18) Has been seeing psychiatrist			1			2		3
Father:								
(19) Depressed/anxious						1		1
(20) Personality disturbance						1		1
(21) Overdose or other method	1	1						2
(22) Has been seeing psychiatrist						1		1
(23) Stress acute		1		2			1	4
(24) Stress chronic (chronic illness)	1	2	3				1	7
(25) Poor housing	4	5	2	0		2	2	15
(26) Financial problems	2	1	1	4		3		11
(27) Out of work		1	1	0			2	4
(28) Poor bonding		1	1			3	1	6
(29) Family involved with police	1	1	1	0		3	1	7
(30) Social service involvement as problem family		2	1	2	1	4	1	11
(31) Member of family on register for non-accidental injury		2	1	1		2		6
(32) Violent household		1		1	1	5	2	10
(33) Twin			2	2				4
(34) Previous cot death						3		3

Table 4 Presence of all adverse family and social factors present in North and Southern Derbyshire related to category of death (A–G)

Category	*North Derbyshire*			*Southern Derbyshire*			*North and Southern Derbyshire combined*		
	Total	*Adverse factors*	*Adverse factors:case ratio*	*Total*	*Adverse factors*	*Adverse factors:case ratio*	*Total*	*Adverse factors*	*Adverse factors:case ratio*
A	20	7	0·35	35	9	0·25	55	16	0·29
B	4	7	1·7	19	40	2·1	23	47	2·0
C	2	4	2·0	9	23	2·5	11	27	2·4
D	8	21	2·6	6	13	2·1	14	34	2·4
E	3	3	1·0	1	9	9·0	4	12	3·0
F	5	17	3·4	8	40	5·0	13	57	4·4
G	0	0	0	9	24	2·6	9	24	2·6
Total B–G	22	52	2·3	52	149	2·9	74	201	2·7

was made to determine whether some specific steps could have been taken to prevent death. The cases were divided into five grades of preventability (table 5). There were considerable differences in the different clinical groups. In 21 of the 23 category B deaths it was felt that intervention could possibly have prevented death whereas in the 14 category D deaths there was none where intervention might have made a difference. Deaths in categories E and F had a similar pattern to those in category B.

Table 5 Possible preventability of death related to category (A–G)

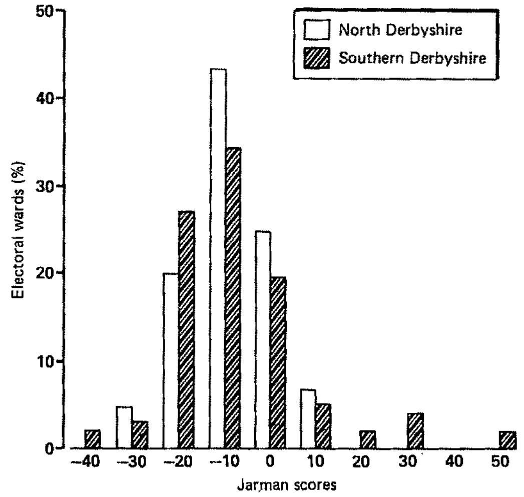
Category	*Inevitable*	*Probably inevitable*	*Possibly preventable*	*Probably preventable*	*Don't know*	*Total*
A	38	16			1	55
B			19	2	2	23
C		1	2		8	11
D					14	14
E			2	1	1	4
F			6	6	1	13
G			2		7	9
Total B–F		1	29	9	26	65

When comparing North and Southern Derbyshire (table 6) for adverse social factors it was found that they were absent among the probably inevitable deaths in the same proportion (81% and 83%). Where deaths were categorised as possibly or probably preventable Southern Derbyshire showed a greater proportion with definite adverse factors, 64% against 36%.

All of the deaths were identified to their local electoral wards and to the Jarman deprivation

Table 6 Preventability and adverse social factors. Results are number (%)

Preventability of death:adverse social factors	*North Derbyshire*	*Southern Derbyshire*	*North and Southern Derbyshire combined*
Inevitable/probably inevitable:			
Absent	17 (81)	29 (83)	46 (82)
Possibly	1 (5)	3 (9)	4 (7)
Definite	3 (14)	2 (6)	5 (9)
Not known	0	1 (<3)	1 (2)
Total	21 (100)	35 (100)	56 (100)
Probably/possibly preventable:			
Absent	2 (18)	4 (14)	6 (15)
Possibly	4 (36)	5 (18)	9 (23)
Definite	4 (36)	18 (64)	22 (56)
Not known	1 (>9)	1 (4)	2 (5)
Total	11 (100)	28 (100)	39 (100)



Jarman scores for electoral wards in Derbyshire.

indices of the ward. When the distribution of the Jarman scores of the electoral wards of North and Southern Derbyshire are compared (figure) two features are apparent. First, in both health authorities the most prevalent scores are in the range of −10 to 0 and second, Southern Derbyshire contains a wider range of deprivation scores than does North Derbyshire. North Derbyshire contained no electoral wards with Jarman scores over 20 whereas Southern Derbyshire contained eight.

Discussion

The postperinatal mortality rate is one of a series of indices that a health district uses to assess its performance in the field of child care. The Department of Health has produced a series of performance indicators for districts but does not indicate what deviation from the national average should lead to inquiry and action.[4] The initiative for this study came from Southern Derbyshire where over a number of years the infant postperinatal mortality rate was significantly higher than the national average and that in North Derbyshire ($p=<0{\cdot}01$). In the two years under study the postperinatal death rate in North Derbyshire was 4·77/1000 live births and that in Southern Derbyshire was 6·1/1000 live births, the one above and the other below the national average.

When the deaths were grouped into those probably not preventable and those possibly preventable after birth, the former rates were remarkably similar in North and Southern Derbyshire, 2·16 and 2·3/1000 live births respectively, apparently randomly distributed through North and Southern Derbyshire. This distribution of deaths in the two districts occurred despite all the non-white deaths occurring in Southern Derbyshire. We feel justified in using this group of deaths as controls for the possibly preventable group of deaths where differences in rates occur. The overall differences in the mortality rates in the two districts lay largely in those that we designate category B deaths. The rate of category B deaths in Southern Derbyshire was 1·3/1000 live births compared with 0·46 in North Derbyshire. A similar difference is seen in category C but not in categories D, E, and F. The numbers of cases involved do not make these differences significant. However when we analysed the deaths in category A compared with those from all other categories from the point of view of the presence or absence of 34 adverse factors, considerable differences were noted.

A very wide range of factors was found (table 3). The overall adverse factor/case ratios were similar between North and Southern Derbyshire. Different categories of deaths have different ratios. In the category A deaths there were only 0·29 factors/case (0·35 in the north and 0·25 in the south). All of the other categories showed more than two adverse factors/case, the highest being category F with 4·4 followed by E with three. The numbers of adverse social factors gives only one side of the picture. The presence of factors has to be related to the individual death and this can only be undertaken by a complete confidential inquiry.

Since the Court report[5] there have been a number of studies suggesting that child mortality is related to many factors[6–9] and studies of child deaths support this.[10 11] The confidential inquiries often revealed features and incidents where incidents leading to probable intervention could have taken place. These points of intervention have already led to local action. Individual cases are not reported at length here as many could be identifiable but details of some have been reported elsewhere.[12]

When we looked at the distribution of the Jarman scores of all wards in North and Southern Derbyshire there were no wards in North Derbyshire with a Jarman score of over 20 and we were able to correlate the areas of high mortality with the Jarman score.[13] This information helps those who can use the Jarman score to direct general family care, but the factors that go to the production of this score are not themselves the direct causes of the deaths[14 15] and the latter are only available through the confidential inquiries.

The evidence we have obtained suggests that there are different levels of preventability in the different clinicopathological groupings within the infants presenting as unexpected deaths (table 5). The most striking feature was that the group which revealed no preventable deaths was that showing non-significant pathology (category D), what may be termed 'true sudden infant death', and that this showed similar rates in North and Southern Derbyshire. The categories that showed the greatest number of possibly preventable deaths were the B, E, and F. Those in category B are deaths where treatable factors are present and these constitute the group of the cot deaths where prevention is, with our present knowledge, most practicable and is the group that largely explained the different death rates in North and Southern Derbyshire.

The category E and F deaths are the most controversial but as they constituted over 10% of the deaths in this study they need comment. The preventable factors identified in these families are those associated more with the work of social services than with health services. In the population of Southern Derbyshire a high rate of cot death has been demonstrated in the siblings of families on the child abuse register.[16] Their identification and prevention would seem to lie in the field of child abuse. This needs further study.

This project set out to use confidential case studies to determine factors to explain the continued higher postperinatal mortality rate in Southern compared with North Derbyshire. It was found that there was no difference in the rates of the inevitable deaths in the two districts or in the rate of completely unexplained cot deaths. The differences lay in the partially explained cot deaths (categories B and C). Any attempt to reduce postperinatal mortality in Southern Derbyshire needs immediate focus on these two categories of death.

This study pre-empted the Department of Health recommendation for confidential inquiry and demonstrates the use of such inquiries.[17] It also supplies supplementary information that is necessary for taking action on information such as that presented by Pharoah and Alberman.[18]

The use of the confidential inquiry has been of such local benefit, both in identifying the areas where possible prevention of death lies and in providing sites of action, that it is being continued in Southern Derbyshire as part of the community child care audit.

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Long term health implications of fitness and physical activity patterns

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Abstract

Northern Ireland has the highest incidence of coronary heart disease (CHD) in the world. The physical fitness, activity patterns, health knowledge, attitudes, and dietary habits of a random, stratified sample of 3211 Northern Irish children, comprising 1540 boys and 1671 girls, age range 11–18 years were examined. At all ages boys were significantly more active than girls. The most important finding was an appreciable decline in physical activity levels after the age of 14 years reaching extremely low levels in older girls. While 75% of exercise taken was not related to school, physical education classes constituted the only exercise taken by one third of pupils. Girls had healthier nutritional habits and were more inclined to employ weight control measures than boys. There was a preponderance of children with a higher body mass index indicating a tendency to obesity in the child population. Over 20% of school leavers of both sexes regularly smoked cigarettes and 20% regularly drank alcohol. The postulated relationship between childhood inactivity, adult sedentary lifestyle, and increased risk of CHD raises serious cause for concern regarding the future cardiovascular health of many children.

An unhealthy diet, cigarette smoking, and lack of exercise are implicated in the development of coronary heart disease (CHD).[1] It is a matter of great concern that today's children may be acquiring such habits and therefore a future risk of CHD at least as great as that of the present generation of adults. Northern Ireland has had the highest incidence of CHD in the world[2] and the purpose of this paper is to report the findings of a recent survey of the fitness and lifestyles of Northern Ireland children. In the latter part of this century there has been a dramatic reduction in the amount of physical activity performed in daily life because of the use of motorised transport and a plethora of labour saving devices. It is now possible for the great majority of both children and adults to get through every day of their lives with a minimal amount of physical activity.

It is firmly established that lack of sufficient and appropriate exercise is a major risk factor for CHD. In a thorough examination of the literature Powell *et al* reviewed 43 of the most rigorous epidemiological studies and concluded that an inverse relationship between physical activity and CHD could be identified in over two thirds of the studies,[3] and this postulate has received support from more recent work.[4 5] Although studies have not demonstrated a cause and effect relationship between lack of exercise and CHD, it has been consistently shown that adults who are more physically active have a lower risk of cardiovascular disease than those who are not.[6–9]

Data from a number of studies suggest that risk factors for cardiovascular disease can be identified in children and that most of the risk factors track into adult life.[10–13] The Bogalusa heart study, the most extensive study of risk factors for CHD beginning in early life, has shown that the extent of aortic fatty streaks is strongly related to serum cholesterol concentrations in the young.[14] Physical activity has been shown to improve the lipid profile and this, together with other possible mechanisms, has the potential to protect against heart disease.[15] Encouraging physical activity and the pursuit of fitness in children may therefore have significant health benefits.

The Northern Ireland Health and Fitness Survey (NIHFS) was a national survey commissioned to investigate the activity levels, physical fitness, attitudes, dietary habits, and health knowledge of Northern Irish schoolchildren.

Subjects and sampling

All secondary schools in Northern Ireland (n=256) were grouped according to pupil sex, perceived religion, and selection category (grammar or secondary modern/comprehensive). Each school was given a weighting according to pupil numbers and a random selection of 20 schools was chosen to provide the widest range of pupils in each age/sex group. In each school the age of all children on the school roll was calculated for that school's test week and a random selection of children from each age group was made. The variability of each fitness test was assessed during a pilot study and from examination of the width of the 95% confidence intervals for the median, a target sample size of 200 for each age/sex group was considered adequate for the purposes of the study. A total of 3211 children (1·25% of the age population) was tested. Based on pilot study experience all strata were oversampled by 20% to allow for non-consent or absence from school (table 1). As most children of 17 and 18 years do not attend school, results from these age groups cannot be considered as necessarily representative of the whole population.

METHODS

Written consent was obtained from the parents of all children participating in the study and the

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Table 1 *Numbers of children tested and response rates*

Age (years)	*Children tested*				*Response rate (%)**	
	No of boys	*Mean age*	*No of girls*	*Mean age*	*Boys*	*Girls*
11	223	11·7	222	11·7	87	85
12	209	12·5	233	12·5	85	89
13	211	13·5	225	13·5	89	83
14	207	14·4	223	14·3	74	80
15	215	15·5	221	15·5	63	70
16	209	16·4	226	16·4	62	67
17	181	17·5	202	27·5	67	67
18	85	18·3	119	18·3	64	63
All	1504		1671		72	75
Total No samples		3211			74	

*Response rates were calculated using the formula:

$$\frac{\text{No of children tested} \times 100}{\text{No of children approached}}$$

Children who were originally sampled, but who could not be contacted or had left school, have been omitted from the calculation.

protocols of all tests were approved by the medical ethical committee of the Queen's University of Belfast. All parents completed a medical questionnaire to determine their children's suitability for fitness testing.

LIFESTYLE QUESTIONNAIRE

This questionnaire collected data on physical activity, diet and nutrition, health knowledge and beliefs, leisure activities, exercise enjoyment and participation, alcohol and tobacco use, and family influences on behaviour.

An administrator supervised the questionnaire completion and gave assistance when appropriate. Strict confidentiality was maintained and this was emphasised to the children.

ANTHROPOMETRY AND FITNESS

Tests were selected from the Eurofit test battery and, with one exception (endurance run), all tests were carried out according to the protocols of the Eurofit handbook.[16] Height, weight, skinfold measurements, and the endurance run were performed in the mornings, and tests of flexibility, leg power, trunk strength/endurance, handgrip strength, and running speed/agility tests were performed during the afternoons. The nine tests were administered in the above order throughout the survey. Each test was administered, and results recorded, by the same tester with the exception of the test for handgrip strength, which was administered by the school liaison teacher, after suitable training by the test team.

Height was measured using a Holtain portable stadiometer and weight using Weylux portable beam scales. Skinfold thicknesses were measured using Harpenden fat calipers at mid-bicep, mid-tricep, subscapular, and suprailiac sites on the right hand side of the body.

Endurance running ability was measured using a progressive, 20 metre shuttle run test, adapted specifically for use with children by the physical education department at the Queen's University of Belfast.[17] The test requires children to run 20 metre laps in time with a prerecorded audio signal. Running speed increases as the test progresses and the child drops out, or is withdrawn, when he/she can no longer maintain the required pace.

Flexibility was measured using a sit and reach test, which measures combined shoulder, trunk, and hamstring flexibility. Leg power was measured using a standing broad jump test using a wooden take off board with a landing mat graded in centimetres. Abdominal strength/endurance was measured as the number of sit ups the child could perform in 30 seconds. Sit ups were performed with hands clasped behind the head, the knees bent, and the feet securely held by a partner. Handgrip strength was measured using a grip dynamometer. The dynamometer was held by the side of the thigh while in a standing position and squeezed as hard as possible for 2 or 3 seconds. Running speed was measured using a 10×5 metre shuttle run. Children were required to sprint between two lines placed 5 metres apart, within a 1·3 metre wide track. The time taken to sprint 10 laps was recorded.

PHYSICAL ACTIVITY

Three methods of assessing children's activity patterns were used. Firstly, children were asked a series of questions about their habitual physical activity (travel to school, school based activities, out of school activities, etc). Answers were coded according to frequency, intensity, and duration, appropriately weighted and an 'activity score' was computed. Secondly, children were asked to indicate which of four descriptions, relating to lifestyles incorporating differing levels of habitual physical activity, fitted them best. Thirdly, children were asked to complete a seven day recall of physical activity, again based on the frequency, intensity, and duration of exercise.

Each method used two descriptions of intensity: that which causes slight breathlessness and that which causes considerable breathlessness. The aim was to achieve a measure of the children's involvement in light to moderate activity and vigorous activity respectively. For both the activity score and the seven day recall children were 'cued' using a time based framework using the structure of a typical school day. This method was felt to be more accurate than cueing by activities, which is the more traditional method.

It should be stressed that such methods cannot accurately quantify physical activity and therefore we can only refer to 'reported involvement' in physical activity, which is likely to be an overestimate. However, the strength of such methods is that they can be used with large numbers of children and can identify similarities and differences in activity levels at different ages and between the sexes.

In addition to reporting the quantity of physical activity, children were also asked questions about their attitudes to sport, physical activity, and physical education. This included questions about whether they enjoyed physical activity, why they did or did not enjoy it, and the role of physical activity in leisure activities.

TEST ADMINISTRATION

All tests were carried out by one test team using one set of equipment and each test was administered at approximately the same time of day. All equipment was regularly calibrated throughout the duration of the test period.

Results

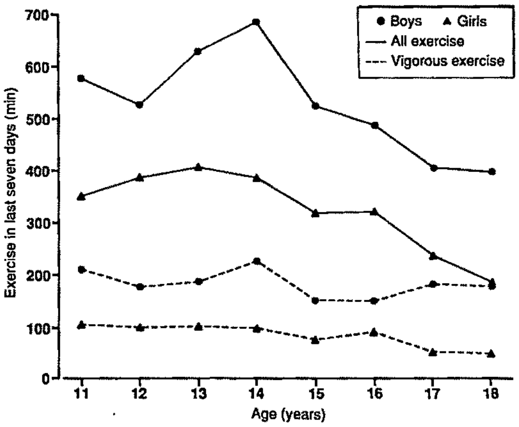
RESPONSE RATES

Response rates by age and sex group are given in table 1. The target sample size of 200 could not be achieved in children aged 17 and 18 years. Information for these age groups should therefore be interpreted with care.

PHYSICAL ACTIVITY

Eighty nine per cent of boys and 84% of girls reported enjoying physical activity of an intensity that caused breathlessness. The commonest reason given in younger children was 'because it's fun' while in older children 'health and fitness' became the most important reason. Two thirds of children who disliked physical activity gave 'discomfort' as the main cause. Seventy nine per cent of boys and 66% of girls indicated an intention to continue playing sport when they left school.

Only 39% of boys and 19% of girls walked to school, whereas 49% of boys and 29% of girls walked home from school. Less than 1% of children cycled regularly to and from school. Less than half the children exercised more than three times per week, but 75% of the children took exercise on at least one evening per week. There was an obvious decline in physical activity with age, most noticeable in older girls (figure). Boys and girls of 17 and 18 years were approximately 50% less active than those aged 11–14 years. While 75% of the activity reported was not related to school, physical education classes were the only source of activity recorded by one third of children.



Weekly time (min) spent taking exercise by boys and girls at ages 11 to 18 years.

LIFESTYLE AND LEISURE

Playing sport was reported as the favourable leisure activity of 47% boys and 23% of girls. An appreciable decline was observed in the older children with only 20% of those aged 18 years reporting sport as a favourite activity falling to as low as 9% of older girls (table 2). 'Chatting with friends' was the most popular activity for older girls (42%) and was the most popular pastime for girls overall (23%). Watching television (15%) and reading (13%) were also highly rated. Thirty per cent of boys and 23% of girls reported having regular jobs, most commonly as shop assistants, working on average 9–10 hours per week. Girls generally spent more time on homework: 66% spent over one hour per night compared with 46% of boys. Two thirds of children went to bed before 11 pm on evenings before school days two thirds stayed up later than 11 pm at weekends.

ALCOHOL AND SMOKING

Fourteen per cent of boys and 11% of girls reported smoking regularly, the incidence increasing most noticeably between the ages of 12 and 15 years so that by 18 years 20% of boys and 28% of girls were regular smokers (table 3). Consumption of alcohol increased around the age of 14 years when 13% of boys and 4% of girls reported drinking alcohol on at least one occasion per week, rising to 25% of boys and 11% of girls at 15 years of age (table 4).

Table 2 Children's favourite leisure activities by age (years). Results are percent of children indicating favourite activity

	11	*12*	*13*	*14*	*15*	*16*	*17*	*18*
No of boys	223	209	211	207	215	209	181	85
No response	22·9	13·9	11·8	13·0	10·7	8·1	1·1	5·9
Watching TV or video	12·6	11·0	15·6	12·1	11·2	14·8	14·9	14·1
Playing computer games	6·7	12·9	7·1	6·8	5·2	3·3	1·7	2·4
Reading for pleasure	1·3	3·3	2·4	1·4	0·9	1·9	5·0	1·2
Chatting with friends	2·7	2·4	3·8	2·4	8·8	13·4	12·2	24·7
Playing sport	44·8	46·4	42·7	45·8	38·1	34·4	39·8	31·8
Doing a job (for money)	4·5	5·3	7·6	7·7	12·6	10·5	10·5	1·2
Helping with jobs in the house	0	0·5	0	1·4	1·4	1·0	0·6	0
Doing homework	0	0·5	0	0	0·5	0·5	1·1	1·2
Other	4·5	3·8	9·0	9·7	10·7	12·0	13·3	17·6
No of girls	222	233	225	223	221	226	202	119
No response	18·0	6·0	10·7	10·3	3·6	3·5	2·0	2·5
Watching TV or video	19·4	21·0	21·8	20·6	17·2	14·6	9·9	10·9
Playing computer games	3·2	6·4	4·0	1·8	0·5	0	0·5	0
Reading for pleasure	9·0	8·6	6·7	6·3	8·1	7·1	9·9	5·9
Chatting with friends	10·4	11·2	15·1	16·6	24·9	37·2	37·1	42·0
Playing sport	25·2	35·6	27·1	22·4	19·9	16·4	17·8	9·2
Doing a job (for money)	1·8	0·4	2·2	4·0	9·0	7·5	3·0	3·4
Helping with jobs in the house	3·2	2·1	2·2	2·2	0·5	0·9	0	0
Doing homework	0·9	1·7	2·7	0·4	1·4	0·4	1·0	1·7
Other	9·0	6·9	7·6	15·2	14·9	12·4	18·8	24·4

DIET AND NUTRITION

Twenty six per cent of children considered themselves overweight and had tried to lose weight. Potato crisps were the favourite snack. Fifteen per cent of children began the day with no breakfast. Sixty five per cent of children ate fruit and vegetables at least three times a week. Seventy five per cent of boys and 86% of girls considered eating less fat to be the most important dietary modification in order to be more healthy.

ANTHROPOMETRY

Height

At the age of 11 years, girls were marginally taller than boys, but boys caught up at the age of 14 years, and by the end of puberty had clearly overtaken the girls (tables 5 and 6). The height of girls levelled off at 14 years, at which time girls had in effect attained their adult height. Boys continued to increase in height up to the age of 16, when a plateau was reached. Boys, at the completion of growth, were 12 cm

Table 3 Cigarette consumption in children in answer to question: how many cigarettes do you normally smoke in a week? Results by age (years) as percent of total at each age

	11	*12*	*13*	*14*	*15*	*16*	*17*	*18*	*All*
No of boys	223	209	211	207	215	209	181	85	1540
No response	2·2	1·9	0·5	1·0	0·5	1·4	1·1	2·4	1·3
None	91·0	93·3	91·9	87·0	82·3	78·0	81·8	77·6	86·1
1–5 a week	4·5	2·9	2·8	3·4	2·3	4·3	2·8	3·5	3·3
5–10 a week	0·4	1·0	0·9	2·4	2·3	1·0	2·2	0	1·4
10–20 a week	0·4	0	3·3	1·9	1·4	3·3	2·2	2·4	1·8
Over 20 a week	1·3	1·0	0·5	4·3	11·2	12·0	9·9	14·1	6·1
No of girls	223	209	211	207	215	209	181	85	1540
No response	0·9	2·6	0·9	0·4	0·5	0	0·5	0	0·8
None	99·1	94·4	94·2	90·1	81·4	85·0	83·2	72·3	88·5
1–5 a week	0	3·1	2·7	4·5	5·9	3·1	2·5	4·2	3·2
5–10 a week	0	0	1·8	1·3	2·7	4·4	352	8·4	2·4
10–20 a week	0	0	0·4	0·4	1·8	3·5	1·5	2·5	1·2
Over 20 a week	0	0	0	3·1	7·7	4·0	8·9	12·6	3·9

Table 4 Alcohol consumption in children in answer to question: how often do you normally drink alcohol? Results by age (years) as percent of total at each age

	11	*12*	*13*	*14*	*15*	*16*	*17*	*18*	*All*
No of boys	223	209	211	207	215	209	181	85	1540
No response	0·9	2·4	0	0·5	0·5	1·0	1·1	2·4	1·0
I never drink alcohol	88·8	77·0	68·7	59·9	47·9	38·3	26·0	21·2	56·9
Less than once a week	5·4	12·9	21·3	26·6	24·7	37·3	35·4	36·5	23·7
Once or twice a week	3·6	4·8	8·5	10·6	24·2	21·1	29·3	31·8	15·2
Three to five times a week	0·4	1·9	0·9	1·4	1·4	2·4	8·3	8·2	2·6
Six or seven times a week	0·9	1·0	0·5	1·0	1·4	0	0	0	0·6
No of girls	222	233	225	223	221	226	202	119	1671
No response	0·9	1·3	0·4	0·4	0·5	0	0·5	0	0·5
I never drink alcohol	97·7	90·6	90·7	79·4	62·9	53·5	42·1	31·9	71·3
Less than once a week	1·4	6·9	5·8	16·6	25·8	34·1	34·2	40·3	19·2
Once or twice a week	0	1·3	3·1	3·1	10·4	11·5	22·8	26·1	8·6
Three to five times a week	0	0	0	0·4	0	0·4	0	1·7	0·2
Six or seven times a week	0	0	0	0	0·5	0·4	0·5	0	0·2

Table 5 Boys' anthropometric and physical fitness characteristics by age (years). Results are mean (SD)

	11 (n=222)	*12 (n=210)*	*13 (n=215)*	*14 (n=208)*	*15 (n=219)*	*16 (n=211)*	*17 (n=180)*	*18 (n=89)*
Height (mm)	1449 (69)	1503 (76)	1566 (82)	1621 (84)	1689 (68)	1734 (70)	1760 (67)	1748 (54)
Weight (kg)	39·7 (7·2)	42·1 (8·8)	46·5 (4·4)	51·7 (10·1)	58·0 (9·5)	64·2 (9·6)	66·5 (9·0)	67·0 (8·9)
Body mass index	17·8 (2·4)	18·5 (2·8)	18·8 (2·7)	19·5 (2·6)	20·2 (2·7)	21·3 (2·7)	21·4 (2·3)	21·9 (2·5)
20 metre shuttle run test (laps)	61 (19)	65 (17)	72 (19)	79 (20)	86 (20)	90 (18)	96 (18)	98 (20)
Sit and reach (cm)	16·5 (6·0)	15·0 (6·5)	16·0 (7·0)	17·0 (6·5)	19·5 (7·5)	22·0 (7·5)	23·5 (8·5)	24·5 (7·0)
Standing broad jump (cm)	145 (19)	150 (20)	161 (23)	169 (25)	183 (24)	195 (24)	200 (24)	205 (22)
No of sit ups completed in 30 secs	22 (4)	23 (4)	24 (4)	25 (4)	25 (4)	26 (4)	26 (4)	26 (4)
Grip strength (kg)	20 (4)	23 (5)	26 (6)	30 (7)	37 (8)	42 (7)	46 (7)	46 (7)
10×5 m sprint (millisecs)	219 (19)	216 (18)	208 (16)	203 (16)	198 (15)	191 (14)	189 (14)	191 (14)

Table 6 Girls' anthropometric and physical fitness characteristics by age (years). Results are mean (SD)

	11 (n=224)	*12 (n=237)*	*13 (n=229)*	*14 (n=226)*	*15 (n=219)*	*16 (n=227)*	*17 (n=200)*	*18 (n=121)*
Height (mm)	1471 (75)	1511 (77)	1563 (67)	1594 (60)	1602 (60)	1620 (59)	1626 (63)	1626 (56)
Weight (kg)	40·6 (8·9)	43·1 (8·8)	48·7 (9·3)	52·9 (7·9)	54·0 (7·4)	56·5 (7·7)	56·6 (6·9)	57·2 (7·6)
Body mass index	18·6 (2·2)	18·8 (2·8)	19·8 (3·2)	20·8 (2·8)	21·0 (2·6)	21·5 (2·7)	21·4 (2·4)	21·6 (2·6)
20 metre shuttle run test (laps)	41 (13)	47 (14)	48 (15)	49 (16)	49 (14)	50 (15)	50 (16)	44 (14)
Sit and reach (cm)	20·5 (6·5)	20·5 (6·0)	21·5 (6·5)	24·5 (6·5)	25·0 (6·5)	25·0 (7·0)	26·0 (7·5)	23·5 (7·0)
Standing broad jump (cm)	131 (19)	136 (19)	140 (21)	144 (22)	145 (21)	147 (22)	151 (22)	144 (19)
No of sit ups completed in 30 secs	19 (4)	20 (4)	19 (4)	20 (4)	20 (4)	20 (4)	19 (5)	19 (5)
Grip strength (kg)	19 (4)	20 (4)	23 (4)	26 (4)	27 (4)	28 (5)	29 (5)	27 (4)
10×5 m sprint (millisecs)	235 (18)	226 (20)	227 (17)	224 (19)	221 (22)	220 (19)	220 (20)	232 (18)

taller than girls. The largest increase in height between successive age groups was 12–13 years for girls and 13–14 years for boys (however, boys increased in height uniformly from 11–16 years). This reflects the earlier adolescent growth spurt experienced by girls, known to occur two to three years earlier than boys.

Weight

Children's development in terms of weight closely mirrored their development in terms of height (tables 5 and 6). At 11 years, girls were 3 kg heavier than boys, but boys caught up by the age of 14, and by the end of puberty boys were 10 kg heavier than girls. The largest difference in weight between consecutive age groups was 12–13 years for girls (6·4 kg), and 14–15 years for boys (6·7 kg). As with height, girls' weight levelled off at 14 years, whereas with boys, no plateau was seen until 16–17 years.

Body composition

In boys, little change was seen in the sum of four skinfold measurements during the adolescent years. However, boys experienced redistribution of fat away from the biceps and triceps towards the subscapular and suprailiac sites, that is, from the arms to the trunk. There was an increase in body mass index (weight in kg/height in m^2) with age (table 7). As body mass index is normally used as a measure of fatness, this suggested that boys were increasing their fat mass. This conflict may be explained by a greater increase in both bone and muscle mass in boys, compared with height. This would cause an increase in body mass index that was not due to fat deposition.

Girls of all ages had a greater amount of adipose tissue than boys. A steady increase could be seen up to the age of 14 years, at which time a plateau was achieved. There was an appreciable increase from 13–14 years, that is, towards the end of the adolescent growth spurt. The increase in body mass index in girls may partly reflect an increase in lean tissue, but the greatest component of the increase is likely to be the extra adipose tissue acquired by girls during puberty.

Girls showed a greater range of adiposity than boys at all ages, and both sexes showed a greater range of values before puberty than after. Boys and girls of all ages showed a greater range of results between the 50th and 80th centile than between the 20th and 50th centile, indicating that there is a greater range of 'fatter' children than 'leaner' ones.

PHYSICAL FITNESS (TABLES 5 AND 6)

Endurance running ability (20 metre shuttle run)

Clear differences between the sexes could be seen in the results of the 20 metre shuttle run test. Boys outperformed girls at all ages, with a 60% difference at 11 years and a 136% difference at 18 years. Girls showed no increased ability after the age of 12 years, whereas boys showed a steady increase until the age of 17–18 years. Boys showed a larger range of scores at all ages.

The lack of improvement by girls is likely to be a consequence of increased adiposity. If this is a more significant factor than improvements in cardiovascular fitness then no improvement in endurance running ability will be seen. Boys, however, not only have the benefit of maintained or reduced fat levels, but also acquire additional aerobic capacity as a result of their increase in muscle mass.

Flexibility (sit and reach)

Both boys and girls were at their least flexible at the age of 12 years. Boys then showed a steady increase from 12–18 years with a considerable increase at 13–14 years (3 cm). Girls also increased their flexibility from the age of 12 years, but the increase was not so noticeable. However, girls outperformed boys at all ages,

Table 7 Body mass index (weight in kg/height in m^2) by age (years)

	11	*12*	*13*	*14*	*15*	*16*	*17*	*18*
No of boys	222	210	215	208	219	211	180	87
Centiles								
90	21·0	21·7	22·6	22·6	23·7	24·5	24·8	25·0
80	19·6	20·5	20·8	21·8	21·8	23·2	23·3	23·8
70	18·7	19·5	19·8	20·7	21·1	22·5	22·3	23·0
60	18·0	18·7	19·1	19·7	20·4	21·8	21·6	22·2
50	17·4	18·0	18·5	19·2	19·7	21·0	21·0	21·7
40	17·0	17·2	17·7	18·7	19·2	20·3	20·6	21·2
30	16·4	16·6	17·1	18·2	18·7	19·7	20·0	20·6
20	15·8	16·2	16·4	17·5	18·2	19·0	19·4	19·8
10	15·1	15·6	15·8	16·4	17·4	18·4	18·9	18·7
Mean (SD)	17·8 (2·4)	18·5 (2·8)	18·8 (2·7)	19·5 (2·6)	20·2 (2·7)	21·3 (2·7)	21·4 (2·3)	21·9 (2·5)
No of girls	224	237	229	226	219	227	198	121
Centiles								
90	23·3	22·5	23·9	24·3	24·4	25·4	24·1	25·3
80	20·7	20·5	22·0	22·9	22·9	23·2	23·0	23·4
70	19·7	19·7	20·8	21·9	22·0	22·5	22·4	22·5
60	18·8	19·2	19·8	21·3	21·5	21·8	21·8	21·8
50	18·2	18·4	19·2	20·5	20·7	21·1	21·2	21·3
40	17·3	17·9	18·6	19·7	20·2	20·5	20·6	20·8
30	16·6	17·1	18·0	19·0	19·7	19·9	20·2	20·2
20	16·0	16·5	17·5	18·5	18·7	19·4	19·5	19·3
10	15·3	15·6	16·5	17·7	17·9	18·5	18·8	18·5
Mean (SD)	18·6 (3·2)	18·8 (2·8)	18·8 (3·2)	20·8 (2·8)	21·0 (2·6)	21·5 (2·7)	21·4 (2·4)	21·6 (2·6)

although the gap between the sexes narrowed from the age of 14 years, until there was no apparent difference at the age of 18 years. However, this apparent equality could be a sampling artefact.

The improved flexibility with age seen in both sexes may be explained by changes in bone ratios during puberty.

Trunk strength/endurance (sit ups)

Boys outperformed girls at all ages, with boys showing a gradual increase from 11–18 years and girls showing no increase at all. This difference may be explained by the girls' increased adiposity because extra fat, especially if acquired on the upper body, will adversely affect performance.

Handgrip strength (grip dynamometer)

No sex differences in grip strength were evident between the ages of 11–13 years, with both sexes showing a gradual increase in performance. From 14 years onwards, however, boys showed an appreciable increase until the age of 17 years, whereas girls showed only a small increase. The gap between boys' and girls' performance widened continuously with age.

Leg power (standing broad jump)

No sex differences in leg power were evident between the ages of 11–13 years, with both sexes showing a gradual increase with age. From 14 years onwards, however, boys showed an appreciable increase in performance, whereas girls showed only a small increase.

Speed/agility (10×5 metre shuttle sprint)

Boys outperformed girls at all ages. Both boys and girls showed an increase in performance from the age of 12 years, with girls showing a modest increase, whereas the boys' increase was more noticeable.

GENERAL SUMMARY—ANTHROPOMETRY AND FITNESS

The height and weight of boys and girls increased steadily during the school age years. In boys, it seems increased weight resulted predominantly from an increase in lean tissue, whereas in girls it resulted predominantly from an increased fat mass.

The motor fitness of boys improved appreciably with age. It is likely that the principal component of the improvement was increased stature and muscle mass. The motor fitness of girls improved less dramatically and in some cases there was no improvement. Boys outperformed girls in the motor performance tests at all ages, and it is interesting to note that this was true of the prepubertal children. At this age girls were larger and may be thought to have an advantage in terms of performance. The fact that they performed worse than the boys may reflect more frequent participation in sports by boys, who therefore acquired improved coordination and neural adaptation. Alternatively, it may be that girls were less motivated to perform maximally than boys, or that the tests had a skill element, which might give boys an advantage.

Girls' performances in the endurance run and sit ups tests showed no improvement with age. The main reason for their lack of improvement, and minimal improvements in some other tests, was likely to be increased adiposity.

Discussion

Given the proposed link between physical activity and health,[18] the most significant findings of this survey are the age and sex differences in physical activity levels. It appears to be the process of exercising that confers health benefits and not the ability to perform fitness tests. Although there are a significant number of very active children, especially in the younger age groups, there is also a large group of children who take part in very little physical activity. In both sexes there is an appreciable decline in physical activity after the age of 14 years and the very high percentage of inactive girls is of particular concern. There is an important interface where doctors and teachers can target these children to prevent the onset of hypokinetic disease. Because of the lack of comparative standards no claims that children are any less active than they once were can be substantiated.

In stature, body composition, and physical fitness Northern Irish children are similar to their age matched peers in other western industrialised countries: Australia,[19] New Zealand,[20] Canada,[21] and the USA.[22] There is no evidence that children are any less fit now than they were in past generations.[23]

It is suggested that fitness in children may be largely genetically determined,[23] and more evidence has been found for a decreased cardiovascular risk associated with physical activity than with physical fitness. This indicates that physical activity of a level less than that needed to improve physical fitness may confer significant health benefits.[18]

Physical activity may protect against heart disease by improving the lipid profile,[15] maintaining blood pressure within safe limits,[24] and controlling body weight.[25] The protective effect of exercise, in terms of cardiovascular disease, appears to be related to the total amount of energy expended during regular physical activity rather than to the amount of vigorous exercise taken.[26] Also, improvements in strength, muscle endurance, body composition, flexibility, self image, and longevity can result from levels of exercise well below those recommended for improving cardiovascular fitness.[27]

It has been suggested that children who engage in regular physical activity are most likely to become active adults[28 29] and that there is a behavioural tracking of activity levels from childhood to adulthood.[30] It is therefore vital that our children are encouraged to acquire positive attitudes towards regular physical activity.

It is encouraging that girls appear to have a reasonable knowledge of nutritional matters and that the concept of lowering fat consumption is recognised as part of a healthy diet by both boys and girls. It indicates that preventive health messages do register with children. However, it appears that the combination of energy restriction and physical exercise to bring about weight loss has not been effectively communicated to children, although this is recognised to be a more effective and permanent means to fat loss than energy restriction alone.[31 32]

Smoking cigarettes is clearly established as one of the major risk factors in CHD and serious respiratory disorders.[1] Both this and previous studies[33] suggest an incidence of between 20% and 25% in school leavers. Regular alcohol consumption in schoolchildren also has serious implications for health in adult life. Health education efforts aimed at informing children of the long term health implications of tobacco and alcohol abuse remain a priority.

FUTURE RESEARCH

Why so many children, especially girls, are inactive is one of several questions that require further study. It may be important to identify groups of children who display more than one risk factor. The clustering of risk factors is a well documented phenomenon[34] and children prone to high risk might be targeted accordingly. The environmental, social, and psychological reasons that underlie such clustering needs to be identified. The final step is to develop an effective health education strategy targeted at the high risk groups. Extensive information from this baseline study is available to enable educationalists and paediatricians to press for such a preventative health programme in children.[35]

CONCLUSION

This survey has shown that a significant number of Northern Irish children undoubtedly display a number of adverse behavioural traits which, if continued in to adult life, may place them at considerable risk of future ill health.

Children choose their leisure pursuits, including exercise and sport, eating habits, and alcohol and tobacco use according to their perceived relative benefits and attractions. Leventhal has argued that children are no more likely to learn from or act upon health information than adults.[36] Physical activity programmes will therefore only be effective if children become intrinsically motivated to exercise on their own.[37–39] It is important to ensure that their experience of health education, exercise, physical education, and sport are positive to enable children to make informed choices based on knowledge and understanding. The results of this survey should be a stimulus to parents, family doctors, school medical officers, community paediatricians, educationalists, teachers, and all those who can influence the lifestyles of schoolchildren. In particular we must encourage the adoption of regular physical activity during childhood as a sound basis for acquiring a healthy adult lifestyle.

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Crying babies of the Kalahari

Dr Ronald Barr of Montreal Children's Hospital has contributed much to our knowledge of crying in babies and 'infant colic' (see Archivist 1991:970). In an annotation in *Developmental Medicine and Child Neurology* in April 1990 he summarised what is known about normal crying behaviour.[1] Many studies have shown that fussing and crying (and the two may be biologically different) rise to a peak at around 6 weeks of age then decline to a fairly constant level between 3 and 12 months. There is a diurnal variation with crying clustering in the late afternoon and evening and this too is most marked at around 6 weeks. Although this feature remains fairly constant in different populations of babies, there is considerable interinfant and intrainfant variability. This pattern is true of the duration of crying during the 24 hours but the frequency of crying episodes tends not to show such a strict age relationship. The pattern has been thought to be an innate biological feature of the species unrelated to caretaking practices but Hunziker and Barr in 1986 showed that increased carrying of babies reduced the amount of crying and eliminated the early peak.[2] So is the pattern of crying observed in babies in technologically advanced societies a feature of such societies or a species specific biological characteristic?

The !Kung San people are hunter-gatherers who live in the Kalahari desert in north west Botswana and who were 'anthropologised' in the 1970s. Now Dr Barr has joined forces with an anthropologist, Dr Konner, and two psychologists, Drs Bakeman and Adamson, to publish data gathered in Botswana between 1969 and 1971 and in 1975 (*Developmental Medicine and Child Neurology* 1991;**33**:601–10). !Kung San mothers are supremely responsive to their babies. They hold or carry them for over 80% of the day time and respond immediately to their fussing or crying (over 92% response within 15 seconds). The data show that !Kung San babies also have a peak of crying in the first three months and that there is little difference in the frequency of crying between them and Dutch or American babies but their total duration of crying during the day is about half that of Dutch babies. In 'Western' infants 40% of crying in early infancy occurs between 6.00 pm and midnight. The !Kung San data do not provide information about diurnal variation and it is possible that these babies make up for their relative quietness during the times they were observed by crying at other times during the day or at night.

Present information, therefore, suggests that a peak in duration of crying in the second or third month is characteristic of the human species. Changes in caretaking practices alter the duration but not the frequency of crying. It is suggested that early crying is a reflection of physiological state ('expressive' crying) but later crying is more controlled and response determined ('communicative' crying). Fairly frequent, brief fretting as seen in the !Kung San is probably biologically valuable because it induces positive responses in the caregiver, but prolonged crying as is seen more often in 'Western' babies may provoke negative responses. It is tempting to relate this to non-accidental injury.

ARCHIVIST

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Effects of oral phosphocysteamine and rectal cysteamine in cystinosis

W G van't Hoff, T Baker, R N Dalton, L C Duke, S P Smith, C Chantler, G B Haycock

Abstract

Diurnal variation in leucocyte cystine and the effects of equimolar single doses of oral phosphocysteamine and rectal cysteamine were studied in eight patients with cystinosis, aged 1·8–16·5 years. No significant diurnal variation in leucocyte cystine was found. Absorption of cysteamine was reduced after rectal administration compared with the oral dose: mean (SD) peak concentration 17·2 (6·3) µmol/l *v* 36·4 (5·5) µmol/l at 40 min and mean (SD) area under the curve 22·3 (14·3) *v* 59·4 (33·1) µmol/h/l. Oral phosphocysteamine significantly reduced the mean (SD) leucocyte cystine from 8·09 (0·47) to 3·26 (1·48) nmol ½ cystine/mg protein at three hours. At 12 hours the mean leucocyte cystine was significantly lower than the pretreatment concentration. Rectal cysteamine did not significantly reduce the mean leucocyte cystine concentration. In conclusion, phosphocysteamine suspension may be administered every 12 hours. Rectal cysteamine administration is feasible but higher doses are required before efficacy can be judged.

Nephropathic cystinosis is a rare autosomal recessive condition in which the amino acid cystine accumulates in the lysosomes.[1] Affected children usually present in infancy with impaired growth and features of Fanconi's syndrome.[1] Progressive renal damage occurs and, without renal transplantation, most children die in the first decade.[1] Other tissues are damaged by the progressive cystine accumulation so that the older transplanted patients can develop hypothyroidism, retinopathy, myopathy, pancreatic dysfunction, and dementia.[2–4]

The biochemical abnormality in cystinosis is a defect in the lysosomal transport of cystine, which leads to excessive cystine accumulation within the lysosomes.[1] This can be determined biochemically in a preparation of leucocytes from a patient. Cysteamine has been shown to reduce the cystine accumulation both in vitro and in vivo.[5] It acts by undergoing disulphide exchange with cystine to form the cysteine-cysteamine mixed disulphide, which is transported out of the lysosome.[6] Long term cysteamine treatment in patients with cystinosis has been shown to reduce the rate of progression of renal damage and improve growth.[7] To overcome the unpleasant taste and smell of cysteamine the prodrug, phosphocyteamine, was developed.[8] Phosphocysteamine is rapidly hydrolysed in the stomach to cysteamine, the active form.[9] Despite their use for over 12 years the pharmacokinetics, optimal route, and frequency of administration of these drugs have yet to be determined. We have undertaken single dose studies of the pharmacokinetics and pharmacodynamics of oral phosphocysteamine and rectal cysteamine.

Patients and methods

PATIENTS

Eight patients with cystinosis were studied. Their details are given in table 1. Renal function was stable at the time of study and none had biochemical evidence of liver disease (plasma bilirubin concentration and aspartate transaminase and alkaline phosphatase activities were within normal limits). Informed, written consent was obtained from the parents and from the older children.

STUDY PROTOCOLS

Patients who were already on cysteamine or phosphocysteamine treatment stopped the drug seven days before the study began to allow an adequate 'wash-out' period. Phosphocysteamine was chosen for the oral dose study because most patients find it more acceptable than cysteamine.

Table 1 Patient details

Patient No	*Age (years)*	*Sex*	*Renal transplant*	*Plasma creatinine (µmol/l)*	*Other medication*
1	1·8	M	No	79	Cyproheptadine
2	2·0	F	No	40	None
3	4·5	F	No	79	Indomethacin
4	10·2	M	No	186	None
5	10·6	M	Yes	68	Prednisolone, cyclosporin, captopril
6	13·9	M	Yes	54	Prednisolone, azathioprine
7	16·1	F	Yes	59	Prednisolone, azathioprine, trimethoprim
8	16·5	F	Yes	192	Prednisolone, cyclosporin, azathioprine, atenolol, frusemide

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As palatability was not a concern for the rectal study, and there is no information on rectal hydrolysis of phosphocysteamine, cysteamine was used for this route. Other drug treatment was not altered during the study periods because of the hazards of withdrawing indomethacin in the pretransplant group and immunosuppression in the transplanted children. Food was withheld for eight hours before and for the first three hours of each study but free access to clear fluids was allowed in view of their obligatory polyuria.

In order to study diurnal variation in leucocyte cystine, six patients (numbers 3–8) first had serial blood samples taken for leucocyte cystine determination over a 24 hour period (at 0800, 0900, 1100, 1400, 2000, and 0800). Then patients 2–8 received a 23 mg/kg single oral dose of phosphocysteamine, given as a suspension in 50 ml water in the morning (0730–0830). Because of the unpalatability of the drug 50 ml of either juice or milk were allowed immediately after the drug. Serial blood samples were taken from an indwelling intravenous cannula for measurement of plasma cysteamine concentration (1 ml) at 0, 20, 30, 40 min, 1, 1·5, 2, 3, 4, 6, 12 hours and for leucocyte cystine determination (3 ml) at 0, 1, 3, 6, and 12 hours after the dose. Intake of diet, fluids, and other drugs was similar on both the predose (diurnal variation) and oral dose day.

In a separate study six patients (numbers 1–6), received an equimolar dose (10 mg/kg) of cysteamine, given rectally as a gel. The dose of cysteamine base for each patient was dissolved in 9% methylcellulose gel to a final volume of between 2·5 and 5 ml so that the dose volume was approximately similar for all patients. The gel was tested for stability and kept at 4°C. Before use, it was allowed to stand at room temperature for 30 min. Gel was administered to the patients in either the left lateral or supine position, over two minutes, using a 5 ml syringe (Steriseal) and a fine soft plastic quill (Avon Medicals). The children remained supine for 15 min after the dose. Blood sampling times were the same as in the oral dose study.

The three younger patients (numbers 1–3) who were experiencing severe vomiting and anorexia from oral cysteamine or phosphocysteamine, were offered a trial of regular rectal cysteamine. The starting dose of 10 mg/kg cysteamine once a day was increased as tolerated. Leucocyte cystine concentrations (12 hours after the last dose) were determined at each clinic attendance. Their parents were taught how to administer each dose and kept a diary to monitor adverse reactions. Patients 1 and 2 were also started on oral indomethacin to control polyuria.[10]

The study protocols were approved by the Guy's Hospital ethical review committee.

ANALYTICAL METHODS

Plasma cysteamine was assayed using a modification of the method of Smolin and Schneider.[11] Plasma was separated immediately and stored at −70°C pending analysis. The samples were derivatised using sodium borohydride to reduce all the disulphides. After protein precipitation, cysteamine was separated by high performance liquid chromatography and measured using electrochemical detection. The limit of detection was 1 μmol/l and the coefficients of variation were 12·0, 4·7, and 4·7% at 5, 20, and 100 μmol/l respectively.

Leucocyte cystine concentration was determined by the method of Greene *et al.*[12] The result was factored by the protein content of the leucocyte pellet which was measured by a modification of the Lowry method.[13 14] In our laboratory, the limit of detection of the cystine assay is 0·05 nmol ½ cystine/mg protein and the coefficients of variation are 24·7, 6·0 and 15·2% at 0·06, 3·54, and 8·47 nmol ½ cystine/mg protein respectively. Plasma creatinine was measured using the standard Jaffé reaction.

PHARMACOKINETIC AND STATISTICAL METHODS

Pharmacokinetic parameters were estimated from standard formulae using the BIOPAK software package. For each plasma cysteamine profile the maximum cysteamine concentration (C_{max}), and time at which this occurred (T_{max}), were noted. The area under the plasma concentration time curve ($AUC_{0-6\ h}$) was determined by the linear trapezoidal method. Individual semilog plots of plasma concentration versus time were inspected to determine the appropriate data points from which to calculate the elimination half life ($t½\beta$). Statistical analyses were performed using a two tailed Student's paired *t* test with Bonferroni's correction for multiple analyses. Significance was assumed if $p<0·05$.

Results

All the patients in the oral dose study successfully swallowed the phosphocysteamine suspension. Two patients (4 and 8) suffered vomiting, starting approximately one hour after the dose. There were no other adverse effects. Administration of the rectal cysteamine gel was well tolerated in the younger three children. The older three children who received rectal gel (4–6) expressed a desire to defaecate approximately 15 min after administration, but were able to retain the dose for a further 15 min. No child in the rectal study suffered vomiting, diarrhoea, or rectal bleeding. The smell of cysteamine on the breath was very noticeable after oral dosage but minimal or not apparent after rectal dosage.

The mean leucocyte cystine concentrations for the six patients in whom diurnal variation was studied are shown in fig 1. There was a trend for the leucocyte cystine to fall during the morning but there was no significant change from the baseline concentration at zero time ($p>0·3$ at all time points). Inspection of diet and drug sheets revealed no association between intake and leucocyte cystine.

The mean leucocyte cystine concentrations after oral and rectal doses are shown in fig 2A. After the oral dose, the mean leucocyte cystine concentration was significantly reduced ($p=0·05$) to a minimum of 40% of the pretreatment concentration at three hours. At 12 hours

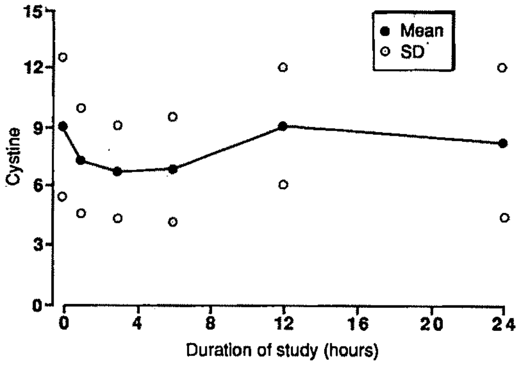

Figure 1 Diurnal variation in leucocyte cystine concentration (nmol ½ cystine/mg protein). Studies were started between 0730 and 0830.

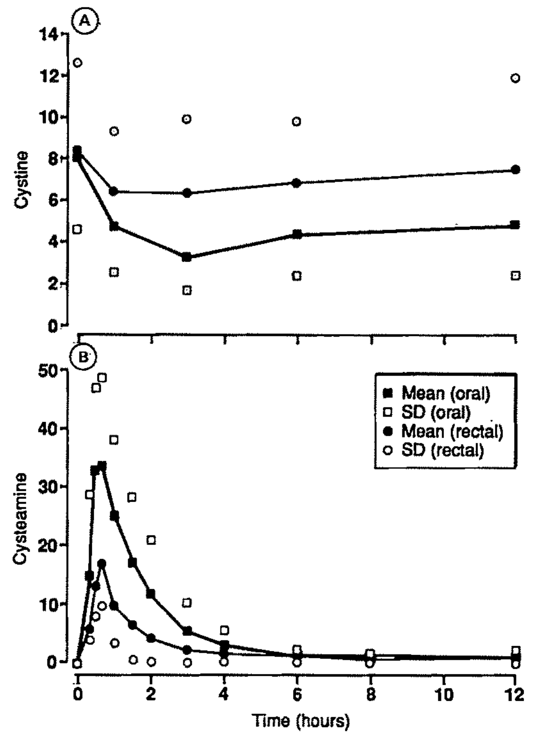

Figure 2 (A) Leucocyte cystine (nmol ½ cystine/mg protein) and (B) plasma cysteamine (μmol/l) after oral phosphocysteamine and rectal cysteamine.

Table 2 Pharmacokinetic parameters after oral administration of phosphocysteamine and rectal administration of cysteamine. Values are mean (SD)

Route	*C_{max} (μmol/l)*	*T_{max} (min)*	*AUC (μmol/h/l)*	*Half life (hours)*
Oral	36·4 (15·5)*	40	59·4 (33·1)**	1·59 (1·48)†
Rectal	17·2 (6·3)*	40	22·3 (14·3)**	0·78 (0·46)†

C_{max} and T_{max} are maximum cysteamine concentration and the time it occurred. AUC is area under the plasma concentration time curve.
*p=0·02, **p=0·03, †p>0·2.

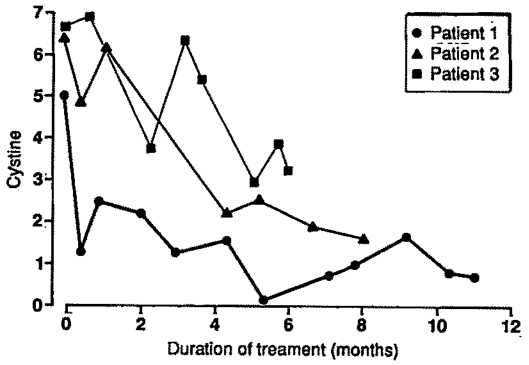

Figure 3 Leucocyte cystine (nmol ½ cystine/mg protein) before treatment (shown at zero), and after treatment with rectal cysteamine. The pretreatment value in patient 1 was obtained before any cysteamine treatment. The pretreatment values in patients 2 and 3 are the means of three and four determinations respectively, taken while on oral phosphocysteamine.

after the dose the mean leucocyte cystine had only reaccumulated to 61% of the pretreatment concentration (p=0·032). There was no significant reduction in mean leucocyte cystine after rectal cysteamine (p>0·1 at all time points).

The mean plasma cysteamine profiles after oral and rectal dosage are shown in fig 2B, and the derived pharmacokinetic paremeters are given in table 2. Inspection of the plasma cysteamine profile for patient 1 in the rectal study showed a slight rise in cysteamine concentration at eight hours, making calculation of pharmacokinetic parameters impossible. The time to peak concentration (T_{max}) was the same in both studies but the mean C_{max} and AUC were significantly reduced after rectal dosage (p=0·02 and p=0·03, respectively). There was no significant difference between the mean elimination half lives, t½β, in the oral and rectal dose studies (p>0·2).

The parents of the children receiving regular rectal cysteamine found no difficulties in administering the doses whereas all three children had refused oral cysteamine or phosphocysteamine (and had also refused other oral medication). Their leucocyte cystine concentrations are shown in fig 3. The adverse reaction diaries showed that the children tended to defaecate 30 min after the dose in approximately 30% of administrations. Their parents noted that halitosis and vomiting after the cysteamine was much reduced. Two of these three patients have now stopped rectal cysteamine and recommended oral phosphocysteamine (one on account of diarrhoea and the other after an episode of minor rectal bleeding).

Discussion

Cysteamine and phosphocysteamine are the only specific drugs available to reduce cystine accumulation in cystinosis. Treatment is started as soon as the diagnosis is made (usually around 1–2 years of age) and continued until end stage renal failure supervenes. We believe that in view of the multisystem complications, there are significantly strong theoretical grounds to continue treatment after renal transplantation. Thus treatment is effectively for life.

Since the accumulation of cystine within the lysosomes is derived from protein catabolism,[15] it might be expected that leucocyte cystine concentration would vary with diet and time of day. Our results show that there is no significant diurnal variation in leucocyte cystine concentrations.

After oral administration of a suspension of phosphocysteamine, cysteamine was rapidly absorbed. Pharmacokinetic parameters for cysteamine have not previously been described. In our study there was considerable individual variation in C_{max}, AUC, and t½β, but in all cases plasma cysteamine was virtually undetectable after six hours. Our plasma cysteamine concentrations are in the same range as those determined by Jonas and Schneider who concluded that the drug should be given in divided daily dosage.[16] Subsequently, cysteamine and phosphocysteamine have been administered every six hours. Smolin *et al* measured the effects of cysteamine and phosphocysteamine on leucocyte cystine for up to six hours and found them to be equally effective.[9] Our results demonstrate that the effect of the drug is more prolonged as the mean leucocyte cystine concentration had risen to only 61% of the pretreatment concentration at 12 hours after the oral dose. A study is planned to confirm whether this prolonged effect of the drug occurs after multiple dosing and with phosphocysteamine capsules instead of suspension. We now advise patients to take phosphocysteamine every 12 hours and we monitor their leucocyte cystine concentrations before a morning dose.

Cysteamine had an unpleasant taste, and after an oral dose the patient's breath smells of free sulphides. A second common side effect is vomiting, typically occurring half an hour or more after the dose. In an attempt to circumvent these problems, we investigated whether rectal administration of cysteamine was feasible and efficacious. The three younger patients receiving rectal cysteamine tolerated the dose without any problems. There was appreciable individual variation in the plasma cysteamine and leucocyte cystine profiles after rectal dosage. Although cysteamine was rapidly absorbed from the rectum, the extent of absorption was reduced when compared with the oral route (table 2). There was no significant effect on the mean leucocyte cystine concentrations (see fig 2A) and this is probably because the older three patients expelled the dose 30 min after administration. Halitosis was noted in two of the patients who had received rectal cysteamine but was minimal compared with that after oral dosage.

The parents of the three patients who received regular rectal cysteamine felt that it was more acceptable than the oral preparation. Compliance improved not only for cysteamine but also for their electrolyte replacements and dietary intake. Their leucocyte cystine concentrations fell towards the accepted therapeutic range (<1 nmol ½ cystine/mg protein; see fig 3). Patient 1 had low cystine concentrations on a comparatively low final dose of cysteamine (20 mg/kg/day) whereas the other two patients required doses similar to those used in oral treatment (70 and 50 mg/kg/day, respectively). For two of the three patients, rectal cysteamine was a 'stopgap' treatment, covering a period in which they were completely intolerant of the oral medication. They are now re-established on oral phosphocysteamine. The short duration of rectal treatment and the small numbers of patients treated preclude any analysis of its effect on renal function.

The results in the present study suggest that, when given as an oral suspension, phosphocysteamine may be administered every 12 hours. Such a reduction in the frequency of administration is of enormous practical benefit to the patients. Rectal administration proved to be feasible and safe. For some children unable to tolerate oral cysteamine or phosphocysteamine, rectal administration may be an alternative.

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Autonomic dysfunction and severe hypoglycaemia in insulin dependent diabetes mellitus

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Abstract

The aims of the present study were to investigate the relationship between severe hypoglycaemia and autonomic dysfunction in diabetic children, and to assess the glycaemic response to an insulin infusion test. In a one year period, 12 of 69 diabetic patients (17%) experienced at least one severe episode of hypoglycaemia, defined as an event which required outside assistance. All patients underwent five cardiovascular autonomic tests. Seven of the hypoglycaemic patients showed three or more abnormal autonomic tests. Among the 57 non-hypoglycaemic diabetics, there was no patient with three or more abnormal tests. In hypoglycaemic diabetics with and without autonomic dysfunction, and in eight healthy age matched subjects an insulin infusion test was performed. A pronounced blood glucose decline and a subnormal increase in heart rate during insulin infusion were obtained in patients with autonomic dysfunction. Thus, severe hypoglycaemia may be due to impaired defence mechanisms against blood glucose decline in diabetic children with autonomic dysfunction.

Hypoglycaemia represents a constant risk for all patients with insulin dependent diabetes mellitus.[1-3] Until recently, hypoglycaemia was considered as an acute event of inadequate diabetes management with no long term consequences. However, recent studies report that irreversible brain damage or intellectual impairment may be the consequence of severe hypoglycaemia.[4-6] Currently available data indicate that severe hypoglycaemic episodes not infrequently accompany conventional insulin treatment and are even more frequent in patients receiving intensified insulin regimens.[1 7 8] Nevertheless, little information is available concerning such episodes in children with diabetes.

There are a number of well established reasons which may explain why diabetic patients run into severe hypoglycaemic episodes. Poor compliance with injection technique, inappropriate insulin dosing with respect to meals and physical activity, and a recent change of insulin dose are factors known to precipitate hypoglycaemia[9 10]; however, one study reported that no cause could be defined in over one third of patients.[11] One assumption is that autonomic nervous system dysfunction may be responsible for increased risk of severe hypoglycaemia, as autonomic activation plays an important role in defence mechanisms against hypoglycaemia.[12-16] In this respect, the importance of disturbed autonomic function is not yet clear in childhood diabetes.

The aims of our present study were to investigate the relationship between severe hypoglycaemia and autonomic nervous system dysfunction in diabetic children treated conventionally with insulin and studied prospectively, and to assess the glycaemic response to an insulin infusion test. With this purpose, we included only those episodes of severe hypoglycaemia that caused loss of consciousness or convulsions and required outside assistance.

Patients and methods

Sixty nine children with insulin dependent diabetes mellitus who had been treated conventionally with insulin (two injections per day) since the onset of disease were considered for inclusion in this study. This represented 58% of the diabetic children seen in our clinic during the study period. All patients were receiving highly purified porcine insulin (Actrapid MC and Monotard MC, Novo-Nordisk) but no other medications. All were healthy except for diabetes, having negligible basal C peptide secretion (fasting C peptide concentration <0·1 nmol/l). The study was conducted prospectively over one year, the patients being seen at our clinic every two months. At each clinic visit, detailed information was obtained from the children and their parents on any episode of severe hypoglycaemia that had occurred since the last visit. Patients were requested to come to the clinic or contact the physician immediately in the event of severe hypoglycaemia, which was defined as loss of consciousness or convulsions and requiring outside assistance. Children with one or more episodes of severe hypoglycaemia during the study period were compared with a non-hypoglycaemic population (table 1). Comparisons between the groups were made by sex, age, duration of diabetes, fructosamine levels determined at each clinic visit, insulin doses, and autonomic function tests.

AUTONOMIC FUNCTION TESTS

Five cardiovascular tests were performed at the start of the prospective study, and one year later. Each diabetic child was examined in the lying position for the mean resting heart rate for a period of one minute, and for beat to beat variation during five maximal inspirations and expirations, for increase in heart rate and fall in systolic blood pressure during one minute standing after the lying position, and for rise in diastolic blood pressure after a one minute sus-

Table 1 Characteristics of diabetic children with and without severe hypoglycaemia. Values are expressed as mean (SD)

	Diabetic children		
	Hypoglycaemic (n=12)	*Non-hypoglycaemic (n=57)*	*Total patients (n=69)*
Hypoglycaemia (events/year)	1·25 (0·5)	0	0·22 (0·3)
Sex (M/F)	4/8	24/33	28/41
Age (years)	13·4 (3·7)	13·8 (3·3)	13·7 (3·4)
Duration of diabetes (years)	6·1 (2·6)*	3·7 (2·4)	4·4 (2·5)
Mean fructosamine (mmol/l)	3·3 (0·6)	3·8 (0·4)	3·7 (0·4)
Daily insulin dose (U/kg)	0·7 (0·3)	0·6 (0·2)	0·62 (0·3)

*p<0·02.

tained maximal handgrip.[17–19] Heart rates were determined with a routine electrocardiographic device (Medicor ER 31–A) by R–R intervals in standard leads; for blood pressure measurements a digital blood pressure device (Omron HEM-400 C) was used. Test results at the start of the study and one year later did not differ significantly. Consequently all results were pooled.

To obtain a reference range of cardiovascular tests, 30 healthy, age matched children were used as a control group. Confidence intervals of 95% (2 SD) from means of control subjects were considered as limits of normality. If the deviation from the mean in the control group exceeded 2 SD, the values of the diabetic children were considered as abnormal.[20]

INSULIN INFUSION TEST

The hypoglycaemic patients and eight healthy children matched for age and weight were exposed to an intravenous insulin infusion test. Studies were performed after a 10 hour overnight fast. The patients took their last dose of regular insulin at 17.00 h followed by their usual meal at 17.30 h and a snack at 21.00 h. Their evening dose of intermediate acting insulin was omitted. To maintain an overnight normoglycaemia in the diabetic subjects, variable rate intravenous infusions of insulin and glucose were started at 24.00 h. The rates were adjusted according to frequent blood glucose measurements. At 07.00 h a constant rate intravenous insulin infusion was started (0·02 U/kg/h, Actrapid HM, Novo-Nordisk) and continued for three hours. Subjects were asked before the study to report immediately any symptoms that they thought might be due to hypoglycaemia. During the three hour constant rate insulin infusion period, capillary blood glucose concentration, heart rate, and blood pressure were determined at 30 minute intervals, and the skin was examined for signs of sweating. Venous blood samples were taken at 60 minute intervals for measurement of free insulin and blood glucose. All subjects gave their informed consent to the study which was approved by the local ethical committee.

ANALYTIC METHODS

Capillary blood glucose concentrations were determined by means of a glucose reflectance meter (Ames Company, Division Miles Laboratories), and venous glucose concentrations were measured by the glucose oxidase method. Serum fructosamine was measured by the Roche fructosamine kit. The mean (SD) for non-diabetic children was 2·0 (0·3) mmol/l. Fasting serum C peptide concentration was determined by the Mallincrodt kit (RIA-mat C peptide). The normal fasting value is 0·17–0·99 nmol/l. Plasma for free insulin was treated with polyethylene glycol immediately after separation to precipitate antibody-bound insulin. The supernatant was then assayed within four weeks with a double antibody radioimmunoassay. The sensitivity of the assay is 0·3 mU/l with a coefficient of variation of 0·04.

STATISTICAL ANALYSIS

Data and results are expressed as mean (SD). Data were tested by Student's paired and unpaired t tests. The frequency of cases with abnormal tests between groups was assessed by χ^2 test with Yates's correction. The metabolic clearance rate was calculated as the ratio between the constant insulin infusion rate (μU/m^2/min) and the steady state, plasma free insulin concentration (μU/ml).

Results

Fifteen hypoglycaemic episodes were registered in 12 (17%) patients, and 57 (83%) diabetics had no hypoglycaemia during the one year study period (table 1). There were no significant differences in respect of sex distribution, age, metabolic control assessed by mean fructosamine concentrations, and insulin doses between the two diabetic groups. However, diabetic children with severe episodes of hypoglycaemia had diabetes of longer duration than patients without hypoglycaemia (table 1).

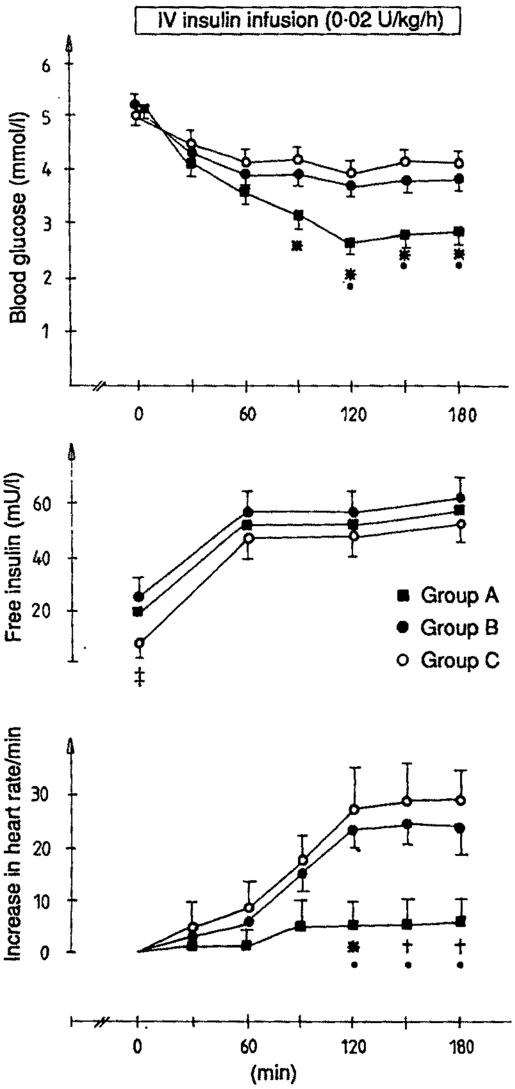
Three or more abnormal cardiovascular tests were obtained in seven of the 12 hypoglycaemic patients, whereas among the 57 non-hypoglycaemic diabetics there was no patient with three or more abnormal autonomic tests (7/12 *v* 0/57, p<0·001). The remaining five patients in the hypoglycaemic group had fewer than three abnormal cardiovascular tests. The two subgroups of hypoglycaemic patients (group A, three or more abnormal autonomic tests, and group B, fewer than three abnormal tests) are characterised in table 2. Sex distribution, age, diabetes duration, metabolic control, and insulin doses were comparable in groups A and B.

Blood glucose and heart rate responses to insulin infusion test as well as plasma free

Table 2 Characteristics of hypoglycaemic diabetics with three or more (group A) and with fewer than three (group B) abnormal cardiovascular tests. Values are expressed as mean (SD)

	Hypoglycaemic patients	
	Group A *(n=7)*	*Group B* *(n=5)*
Hypoglycaemia (events/year)	1·3 (0·5)	1·2 (0·5)
Sex (M/F)	2/5	2/3
Age (years)	13·6 (2·4)	13·0 (3·2)
Duration of diabetes (years)	6·3 (2·9)	5·8 (2·3)
Mean fructosamine (mmol/l)	3·2 (0·6)	3·5 (0·5)
Daily insulin dose (U/kg)	0·73 (0·3)	0·66 (0·3)

insulin profiles in the two groups of patients and in the healthy control group (group C) were compared. As shown in the figure, blood glucose concentrations were similar in the three groups of children before insulin infusion test. Glucose profiles during the insulin infusion test were similar in groups B and C, whereas group A showed a more pronounced glucose decline. The mean blood glucose concentration at glucose nadir was lower in group A than in groups B and C (2·7 (0·3) *v* 3·8 (0·4) and 3·9 (0·4) mmol/l, p<0·01). Group C had lower plasma free insulin concentrations than groups A and B before insulin infusion test (8 (3) *v* 20 (4) and 23 (5) mU/l, p<0·02). The steady state plasma free insulin concentrations were similar in the three groups. The metabolic clearance rates for insulin in groups A (559 (80) ml/m^2/min), B (542 (73) ml/m^2/min) and C (596 (67) ml/m^2/min) were not statistically different. The increase in heart rate during insulin infusion test was similar in groups B and C, whereas group A showed a subnormal heart rate increment (5 (6) *v* 24 (7)/min, p<0·01 and 30 (5)/min, p<0·001). Significant change in blood pressure and increased sweating were not observed in any group studied. Hypoglycaemic symptoms, necessitating cessation of the insulin infusion, did not develop in any subject.



*Blood glucose, plasma free insulin, and increase in heart rate during an intravenous (IV) insulin infusion test in patients with three or more (group A), with fewer than three (group B) abnormal cardiovascular tests, and in normal subjects (group C). *p<0·01, group A v C; •p<0·01, group A v B; †p<0·001, group A v C; ‡p<0·02, group C v A and B.*

Discussion

In this study about 17% of diabetic children treated conventionally with insulin showed one or more severe hypoglycaemic episodes in a single year. This hypoglycaemic group had had diabetes for longer and had greater cardiovascular autonomic dysfunction than the non-hypoglycaemic group. Moreover, there was a relationship between autonomic dysfunction and abnormal glycaemic and heart rate responses to the insulin infusion test in hypoglycaemic patients.

Hypoglycaemia is the most frequent acute complication of insulin dependent diabetes mellitus. The incidence of severe hypoglycaemia in insulin dependent diabetes mellitus is controversial. Some studies report that the severity and frequency of hypoglycaemic episodes is related to the degree of blood glucose control and disease duration.[1 8] In our present study overzealous attempts to achieve normoglycaemia can be excluded as a cause of severe hypoglycaemia because long term glycaemic control did not differ in those with and those without severe hypoglycaemia. However, over-insulinisation in our study may have played a part in a few subjects, but insulin dosages did not differ in those with and those without severe hypoglycaemia.

Hypoglycaemia in insulin dependent diabetic patients results from excessive insulin action, promoting the fall in blood glucose concentration to below the normal range. There are two physiological components of the hypoglycaemic response in both the normal and diabetic individual. The first is the complex of well known clinical signs of declining blood glucose concentration, resulting from autonomic activation. This phenomenon is known as hypoglycaemic awareness. The second component is biochemical in nature: with the decrease of blood glucose concentration, there is normally an increase in counter-regulatory hormone (glucagon, adrenaline) secretion leading to an immediate return of blood glucose concentration to the normal range. It is known that patients with insulin dependent diabetes may lose either their hypoglycaemic awareness, hormonal counter-regulation, or both.[21-23] The mechanism for the loss of these defence systems is unclear. Many reports suggest that hypoglycaemia unawareness and impaired hormonal counter-regulation may be due to disturbed function of autonomic nerves as parasympathetic and sympathetic innervations play a part in glucagon and adrenaline secretion during hypoglycaemia.[12–16] According to our previous study, dysfunction of autonomic nervous system may appear early during the course of childhood diabetes,[20] and subclinical signs of autonomic neuropathy are demonstrable in a considerable proportion of diabetic children and adolescents.[24] Our present study suggests that autonomic dysfunction, at least in part, may be responsible for severe hypoglycaemia in diabetic children. This is in agreement with a very recent study by Hepburn *et al*,[25] who found autonomic dysfunction and hypoglycaemia unawareness coexistently in patients with diabetes of short duration. Nevertheless, further studies are necessary to prove the exact relationship between autonomic dysfunction and impaired defence mechanisms against hypoglycaemia in diabetic children.

With the continuing application of intensified insulin regimens, the question has been raised about an increased risk of hypoglycaemic episodes as a result of the efforts to achieve normoglycaemia in diabetic children. Recurrent and severe hypoglycaemia may be as dangerous as the late complications of diabetes, therefore we have to make an attempt at identifying patients who are at increased risk. Cardiovascular tests may help to identify diabetic children and adolescents in whom intensified insulin treatment may be dangerous and requires more caution.

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Intraosseous infusion for resuscitation

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Abstract

An 11 week old infant who had a cardiac arrest secondary to gastrointestinal haemorrhage and was successfully treated using intraosseous infusion is reported. The child was discharged with no apparent neurological deficit.

Intraosseous infusion was widely practised in the 1940s.[1] There is renewed interest in its use in North America for paediatric resuscitation.[2] This route is successful because the marrow cavity cannot collapse, allowing rapid access to the circulation despite profound hypovolaemia.

Case report

An 11 week old infant was admitted with a history of diarrhoea, vomiting, and weight loss of 0·7 kg (6·5 to 5·8 kg). Viral gastroenteritis was suspected and intravenous rehydration begun. Within 48 hours the child was apyrexial, had resumed feeding, and the intravenous line was removed.

On the third night after admission the child deteriorated and became unresponsive, cold, and cyanosed. Intravenous access proved impossible despite attempts by experienced paediatric staff. The child deteriorated further and became asystolic, necessitating tracheal intubation and cardiac massage; 200 µg of adrenaline was instilled into the endotracheal tube. As further attempts to gain intravenous access were unsuccessful a 19 gauge hypodermic needle was inserted into the right tibia just below the tibial tuberosity, and 250 ml of 4·5% human albumin solution (HAS) was infused rapidly using a 20 ml syringe, followed by 5 ml of 4·2% sodium bicarbonate. A further 200 µg of adrenaline was given via the endotracheal tube.

The colour and peripheral perfusion of the child improved and irregular complexes appeared on the electrocardiogram. At this stage, when approximately 50% of the child's estimated circulating volume had been infused, it was possible to site an internal jugular line. Sinus rhythm was restored, carotid and femoral pulses became palpable, and he began to make respiratory effort.

During further assessment rectal examination revealed bloodstained stool. At laparotomy the bowel was found to contain a large volume of blood. Although no cause for the bleeding was identified, intermittent volvulus was suspected. Eleven days after the cardiac arrest the child was discharged home with no apparent neurological deficit.

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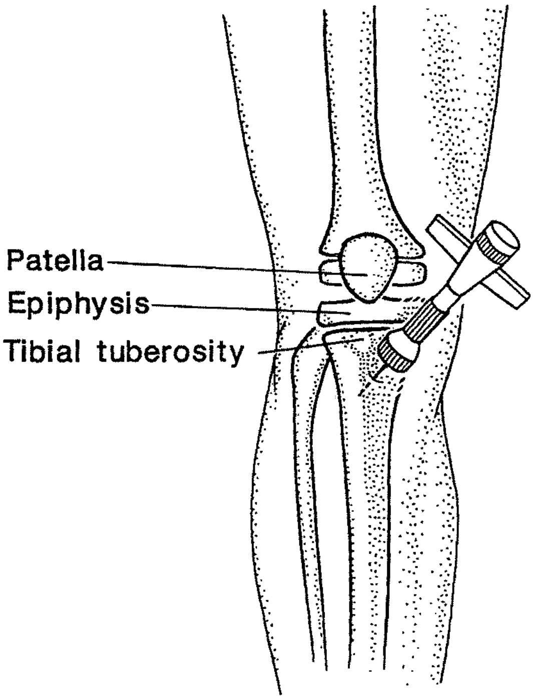
Discussion

Establishing intravenous access in critically ill children may be difficult. Rosetti *et al* found that it took more than 10 minutes to establish vascular access in 24% of paediatric circulatory arrests and in 6% of cases no vascular access was established.[3] In contrast, Smith *et al* recorded an 80% success rate for intraosseous infusion by paramedical staff during the journey to hospital.[4]

The technique of intraosseous infusion consists of sterilising the skin and inserting a 13 to 18 gauge needle into the tibia 1–2 cm below the tibial tuberosity on the medial, flat surface. A boring or screwing action may be required, directing the needle caudally, away from the growth plate (figure). Intraosseous placement is confirmed by loss of resistance, aspiration of bloodstained marrow, and free infusion of fluid.[2] Ideally, a bone marrow infusion needle should be used. In our case the largest needle available was a 19 gauge hypodermic needle.

Other sites for infusion include the distal tibia proximal to the medial malleolus, the distal femur, the iliac crest, and the sternum. In



Insertion site for intraosseous needle.

children under 3 years of age the sternal marrow space is inadequate and there is the risk of mediastinal infusion.[2,5]

The contraindications are osteogenesis imperfecta, osteoporosis, osteomyelitis, ipselateral fracture of the extremity, or local skin infection.[2]

The commonest complication is subcutaneous infusion after failure to enter the marrow cavity. Skin infection has been reported in 0·7% (five out of 694), which is less than that reported with intravascular catheters (3·7%). Osteomyelitis has been reported in 0·6% (27 out of 4270), with an increased risk if the needle is left in situ for a prolonged period. Despite concern about effects on bone growth, no long term side effects have been reported.[5] The deaths attributed to intraosseous infusion have all followed sternal puncture.[2,3]

Blood products, fluids, vasoconstrictors, inotropes, and anticonvulsants have all been investigated using animal models and in clinical practice.[2,6] Although we were reluctant to infuse adrenaline because of fears about the vasoconstrictor effects on the marrow, studies have shown that adrenaline exerts a systemic effect within 20 seconds and atropine exerts its effect more rapidly via the intraosseous route than via the intratracheal route.[6] Sodium bicarbonate can be infused safely, although an increased risk of osteomyelitis has been reported with hypertonic solutions.[2,4]

Fluid flow rates under gravity infusion vary between 1 and 25 ml/minute, but at 40 kPa (300 mm Hg) pressure flow can be increased to 40 ml/minute via a 13 gauge needle.[6]

In the UK intraosseous infusion is seldom used despite the extensive literature on the subject. Even for those with experience of paediatric resuscitation intravascular access may be impossible to achieve, and for the trainee called to resuscitate a child the prospect of placing in intravenous cannula rapidly can be daunting. Intraosseous infusion provides reliable access to the circulation even in inexperienced hands and more than justifies the small risk of complications if intravasular access is difficult. However, this route should only be used in extreme emergencies, in cases where no venous access has been achieved, and after adequate ventilation has failed to improve the child's condition. In this case we are in no doubt that the child would have died if we had not used an intraosseous infusion. We believe that bone marrow infusion needles should be stocked on all paediatric resuscitation trolleys.

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Meningitis caused by human herpesvirus-6

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Abstract

Since the discovery of human herpesvirus-6 (HHV-6) the illnesses associated with it have increased steadily. Two infants with meningitis are reported: both suffered a mild meningitis and serological studies confirmed an acute HHV-6 infection. This report supports a role of HHV-6 in nervous system disease.

Human herpesvirus-6 (HHV-6) was first reported by Salahuddin *et al* in 1986.[1] After its discovery illnesses linked to HHV-6 have been reported and include roseola infantum, hepatitis, lymphadenitis, mononucleosis, atypical polyclonal lymphoproliferative disorder, and haemophagocytic syndrome.[2–4] Here we report two cases of roseola infantum with meningitis, which to the best of our knowledge has not been reported before.

Case reports

CASE 1

A 7 month old girl presented with fever of three days' duration and a mild cough. Physical examination showed only pharyngitis, an appreciably bulging anterior fontanelle, and mild hepatomegaly (3 cm palpable below right costal margin). Lumbar puncture showed 18 mononuclear and 2 polymorphonuclear cells/mm^3. Her cerebrospinal fluid protein concentration was 0·35 g/l and glucose 3·05 mmol/l. During her stay in hospital the peripheral white cell counts ranged from 6·9 and $12{\cdot}0\times10^9$/l and lymphocytes accounted for 60 to 90% of them. Atypical lymphocytes represented 12% of all white cells initially and reached a peak of 25%.

Serological studies showed no evidence of infection of Epstein-Barr virus, cytomegalovirus, or *Toxoplasma gondii*. Virus culture of cerebrospinal fluid was negative. Antibody to HHV-6 was determined by indirect immunofluorescence assay using HHV-6 (U1102 strain) infected J Jhan cells as antigens. The IgG anti-HHV-6 was tested as reported by Salahuddin[1] and IgM anti-HHV-6 as the method of Niederman *et al*.[3] The first serum taken on the fourth day of illness was negative for IgG anti-HHV-6 but positive for IgM anti-HHV-6 (titre 1:10). The second serum taken 11 days later was positive for both IgG anti-HHV-6 (1 : 160) and IgM anti-HHV-6 (1 : 80). A maculopapular rash appeared over her face, scalp, and neck on the fourth day of illness. She became afebrile soon after the rash eruption. No sequela was noted one month after discharge.

CASE 2

This 4 month old boy presented with cough, poor appetite, and high fever. Four episodes of generalised seizure occurred in the next two days with persistent fever. Examination of his cerebrospinal fluid performed on the third day of illness revealed 8 polymorphonuclear cells and 1 mononuclear cell/mm^3. Cerebrospinal fluid protein and glucose concentrations were normal. A peripheral blood smear revealed lymphocytosis (total white cell count was $9{\cdot}6\times10^9$/l, lymphocyte 73%, and atypical lymphocyte 6%). Impaired liver function was noted (aspartate aminotransferase 87 U/l and alanine aminotransferase 50 U/l. His electroencephalogram was normal. A diffuse maculopapular rash appeared over his trunk and lower extremities on the fourth day of illness and his fever soon subsided. Virus culture of throat swab, rectal swab, and cerebrospinal fluid showed no pathogens. The first serum taken on the fifth day of illness was negative for both IgG and IgM anti-HHV-6. The second serum taken 12 days later was positive for both IgG anti-HHV-6 (1 : 160) and IgM anti-HHV-6 (1 : 40). The boy recovered well and no sequela was noted two months later.

Discussion

Both cases underwent a typical course of roseola infantum, that is, high fever for three to four days' duration followed by skin rash eruption and lysis of fever and recovery. Case 1 was neurologically normal and case 2 suffered from repeated seizures. Both had pleocytosis and recovered well. HHV-6 has been known to infect glioblastoma cells[2] and is thought to be a potential cause of nervous system disease. Before the identification of HHV-6 in the aetiology of roseola infantum, encephalitis has been known to occur after roseola infantum.[5] However, the connection between HHV-6 and these reported cases of encephalitis was not certain as no study on HHV-6 was done and enterovirus was incriminated as a possible aetiological factor as it may cause a roseola-like disease. Although the number of diseases linked to HHV-6 are increasing, the connection of HHV-6 with nervous system illness has been shown only by Irving *et al* who reported a 13 month old girl suffering from encephalitis and experiencing brain atrophy six months later.[6]

Our cases had serological evidence of acute primary HHV-6 infection and a search for other viruses failed. Both cases had lymphocytosis and a certain degree of atypical lymphocytosis; one of them fulfilled the diagnosis of mononucleosis syndrome. From the clinical information we believe that HHV-6 was responsible for the full clinical features of these two children.

Roseola infantum is, in a paediatrician's mind, a benign disease. Seizure is not uncommon and is mostly attributed to a febrile convulsion. Though both our cases experienced mild neurological insults, there is no guarantee that HHV-6 causes only mild nervous system disease. Testing for HHV-6 in unexplained neurological inflammatory diseases is therefore important, especially in infants. An additional point is the occurrence of mononucleosis and hepatitis that we observed; both have been reported before.[2 3] This finding supports the view that HHV-6 is capable of causing a variety of illnesses.

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Severe nephropathy in three adolescents with cystic fibrosis

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Abstract

Renal involvement has rarely been reported in patients with cystic fibrosis. We describe severe nephropathy with a rapidly fatal outcome in three adolescents with cystic fibrosis, and evaluate the important repercussions that the nephrotic syndrome had on the precarious clinical situation of these patients.

Despite the general consensus that the kidney is spared in cystic fibrosis and does not present specific lesions, mounting evidence suggests that renal involvement occurs. Numerous and even severe anatomical and pathological changes have been reported in the kidney in patients with cystic fibrosis.[1 2] Glomerular alterations were seen (amyloidosis, glomerulosclerosis, mesangial deposits of immunoglobulins and/or immune complexes, and mesangial proliferation) and also some tubular changes (lymphoplasmacytic infiltrations, fibrosis, and tubular atrophy). Microscopic nephrocalcinosis with intratubular, peritubular, and intracellular deposits has recently been described in cystic fibrosis patients, including very young children (under 1 year).

In contrast to the numerous anatomical and pathological reports, clinical data are scanty. In this paper we describe severe nephropathy with a rapidly fatal outcome in three adolescents and evaluate the unfavourable repercussions of the nephropathy on the precarious condition of these patients.

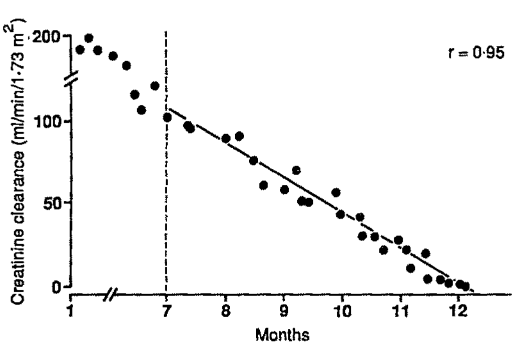

Figure 1 Pattern of glomerular filtration with amyloidosis (patient 1).

Patients and methods

Three non-diabetic patients with a late diagnosis of cystic fibrosis were followed up because of persistent proteinuria. They all underwent percutaneous renal biopsy under urographic guidance.

Specimens for light microscopy were fixed in Bouin's solution, embedded in paraffin, cut into sections of 2–3 μm and stained routinely with haematoxylin and eosin, periodic acid Schiff, and trichrome. Congo red staining was also done when amyloidosis was suspected. Specimens for immunofluorescence were tested with antisera monospecific for IgG, IgA, IgM, C3, C4, C1q, and fibrinogen.

CASE 1

This boy, the second child of healthy, non-consanguineous parents, presented with numerous episodes of bronchopulmonary infections from the first year of life. Cystic fibrosis was diagnosed when the boy was 7 years old, and at the age of 14 he was referred to our centre. He was then in a poor clinical condition. Growth was retarded, and there was respiratory impairment and poor cardiac function. A chest radiograph revealed marked changes consistent with cystic fibrosis. Sputum was colonised by staphylococci, pseudomonas, and candida. Renal function indices were normal (serum creatinine concentration 66·3 μmol/l, blood urea nitrogen 7 mmol/l, creatinine clearance 108 ml/min/1·73 m^2, and normal urinalysis).

One year later a selective mild proteinuria (0·5–1·0 g/day) appeared, which worsened in subsequent months, with a daily protein loss of up to 3 g. The next year a renal biopsy specimen revealed renal amyloidosis. Deposits positive for Congo red were observed at both glomerular and periarteriolar sites. The appearance of proteinuria was accompanied by a mild impairment of glomerular filtration (serum creatinine 114·9 μmol/l, blood urea nitrogen 14 mmol/l, creatinine clearance 63 ml/min/1·73 m^2) and occasional alterations of blood pressure values (systolic pressure up to 140 mm Hg, diastolic pressure up to 110 mm Hg). In the months after biopsy proteinuria worsened, with values stabilised in the nephrotic range, and a nephrotic syndrome and haematuria appeared. At the same time renal failure became progressively more severe (fig 1), reaching the end stage and requiring dialysis the next year. The patient's clinical condition deteriorated rapidly, with severe respiratory impairment, altered fluid and electrolyte balance, poor cardiac function, and severe weight loss. Fifteen days after starting dialysis treatment the patient died of heart failure.

CASE 2

This girl was the firstborn child of healthy, non-consanguineous parents, and from the first months of life had frequent respiratory infections. At the age of 11·6 years the diagnosis of cystic fibrosis was made (sweat test chloride concentration, 97·3 mmol/l). Her clinical condition appeared fairly good (weight, 10th centile; height, 25th centile). Moderate clubbing was observed. A chest radiograph revealed important pulmonary impairment. The electrocardiograph was within normal limits. Moderate alterations were found in respiratory function tests. The coefficient of fat absorption was 47%. Sputum was colonised by staphylococci and pseudomonas.

Over the next four years respiratory function worsened slowly, acute pulmonary exacerbations were frequent, and episodes of haemoptysis occurred.

Renal function indices, investigated when the girl was 17·5 years, were within the normal range (serum creatinine concentration 75·1 μmol/l, blood urea nitrogen 7·7 mmol/l, creatinine clearance 113·4 ml/min/1·73 m^2, no abnormalities at urinalysis). Some months later mild and occasional proteinuria (0·5–0·7 g/day) was observed which during the course of a year worsened to a proteinuria in the nephrotic range (over 6 g/day), non-selective, without alteration of creatinine clearance, haematuria, or hypertension. A renal biopsy specimen, performed when the girl was 18·8 years, demonstrated a typical picture of renal amyloidosis. The sample did not contain glomeruli but amyloid deposits could be seen in the interstitium, particularly at peritubular sites.

After the development of the nephrotic syndrome there was a clear worsening of the clinical condition and nutritional status of the patient. In particular, severe infections were more frequent, it was extremely difficult to maintain fluid, electrolyte, and acid–base balances, and the cardiac condition deteriorated, with subsequent development of severe cardiopulmonary failure. Blood pressure and renal function indices remained normal. The girl died at the age of 18·9 years of heart failure.

CASE 3

This girl was the fourth child of healthy, non-consanguineous parents. In her first few years her symptoms were mainly gastrointestinal, and at the age of 6 years cystic fibrosis was diagnosed (sweat test chloride concentration, 98 mmol/l). The patient was referred to us at age 12 years in a very poor general condition. Chronic cor pulmonale, cyanosis, and clubbing were present, as well as dependent oedema for about 10 days. Growth was retarded. Major pulmonary impairment was shown at radiological examination. Sputum was colonised by pseudomonas and streptococci.

From the first investigations moderate proteinuria (about 1 g/day) was observed, without nephrotic syndrome. Proteinuria was accompanied by haematuria and renal function was not impaired (serum creatinine 40·7 μmol/l, blood urea nitrogen 8·8 mmol/l, creatinine clearance 86 ml/min/1·73 m^2). A renal biopsy specimen showed a typical IgA nephropathy by immunofluorescence. Light microscopy revealed a picture of focal proliferative glomerulonephritis with crescents in 10% of the glomeruli.

For three years proteinuria remained at around 1 g/day, accompanied by occasional haematuria and with renal function indices in the normal range. When the patient was 15·3 years her proteinuria, which was non-selective, became rapidly more severe, reaching concentrations of 10 g/day, with haematuria still present and normal renal function indices. A nephrotic syndrome manifested quickly. The girl's general condition deteriorated with considerable worsening of cardiopulmonary function, a severe weight loss, and blood gas analysis showing respiratory acidosis. She developed hyponatraemia, hypokalaemia, and hypochloraemia. Renal function was normal until a few days before the patient's death when a rise occurred in serum creatinine (106·1 μmol/l) and blood urea nitrogen (34·3 mmol/l). She died of heart failure at the age of 15·4 years.

Figure 2 summarises the pattern of proteinuria in the three patients from its onset.

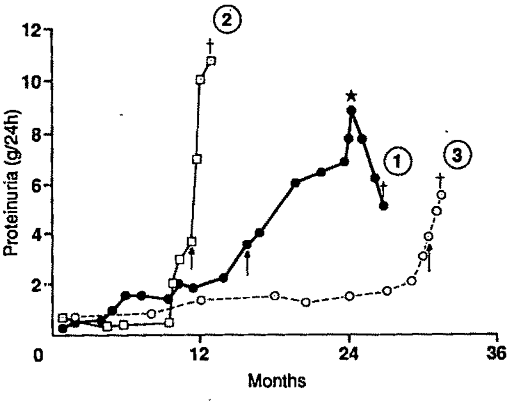

*Figure 2 Pattern of proteinuria with amyloidosis (patients 1 and 2) and with IgA nephropathy (patient 3). † Death; * renal failure; the arrows indicate nephrotic syndrome.*

Discussion

We observed three non-diabetic adolescents with cystic fibrosis who presented severe nephropathy that started as occasional mild proteinuria and evolved rapidly into nephrotic syndrome, with impaired renal function up to end stage renal failure in one patient. The outcome was fatal in all three patients, with deteriorating clinical condition, metabolic and nutritional imbalance, and increased susceptibility to infection.

Although anatomical and pathological changes may be present in the kidneys very early in subjects with cystic fibrosis, several years probably pass before precise clinical manifestations occur, so that nephropathy develops more often in adolescence, as our experience seems to suggest. In all of our cases the diagnosis of cystic fibrosis was made late, thus treatment of infections in their first years of life was probably inadequate. Moreover, the course of nephrotic syndrome in our patients was rapidly unfavourable, and had a devastating impact on their precarious metabolic, nutritional, cardiocirculatory, fluid, and electrolyte balances and on their blood gases. Histological examinations revealed renal amyloidosis in two of them (cases 1 and 2) and IgA nephropathy in one (case 3).

Systemic amyloidosis with renal involvement has been reported in some patients with cystic fibrosis.[3] [4] Secondary amyloidosis is in fact a complication of chronic inflammatory processes such as tuberculosis and bronchiectasis, and it is conceivable that this condition may develop in patients with cystic fibrosis which is characterised by chronic and recurrent respiratory infections. Necropsy was not performed in any of our patients, and thus the possibility that not only the kidney but also other organs such as the heart or liver might have been involved in the amyloid process cannot be excluded. However, radiographs did not demonstrate cardiomegaly in any of the cases, no signs of arrhythmia were revealed by electrocardiographs, and liver function as shown by biochemical data seemed unimpaired.

Experimental models[5] and clinical observations[6] indicate that circulating immune complexes containing IgA have an important pathogenetic role in IgA nephropathy. Patients with cystic fibrosis often have raised immunoglobulin concentrations, especially of the IgG class, related to frequent immune stimulation by recurrent bacterial infections. The role of the underlying disease in the development of IgA nephropathy in patient 3 is not clear. IgA nephropathy is a common type of glomerulonephritis and it is possible that this was just a chance association. Renal biopsy was done three years before the patient became nephrotic and she may have developed amyloid by the time she died.

The overall treatment (chest physiotherapy, nutritional support, and antibiotics) now given to subjects with cystic fibrosis from the time of diagnosis, which is often made in neonatal age or before the appearance of symptoms of the disease, has notably increased the life expectancy of these children, and thus also the possibility of lung or heart and lung transplants in adequately selected cases. The selection of candidates for the transplant programme is crucial for their long term survival, and should include careful monitoring of renal function and signs of renal damage, particularly proteinuria. The patients now admitted to transplant programmes are generally in advanced stages of the disease when secondary complications are more probable. It is very important to exclude the presence of amyloidosis in these subjects. In our opinion, even the mild and occasional proteinuria that is sometimes observed in cystic fibrosis children merits particular attention, with the aim of promptly identifying patients at risk of progressively severe renal impairment and of prescribing appropriate treatments to prevent or at least delay severe clinical manifestations.

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Nutritional manipulation in the management of dumping syndrome

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Abstract

Two children with Nissen's fundoplication and either gastrocystoplasty or pyloroplasty developed dumping syndrome. Correction of their blood glucose abnormalities, resolution of symptoms, and weight gain were effectively achieved by addition of fats and uncooked corn starch (50 g/l) to their feeds.

There is a paucity of literature regarding the prevalence and optimal management of dumping syndrome in children. This results from the rapid gastric emptying of a carbohydrate meal, causing hyperglycaemia followed by reactive, symptomatic hypoglycaemia. Dumping syndrome in children has been described almost exclusively as a postoperative complication of Nissen's fundoplication.[1–3] Several therapeutic approaches have been tried with mixed results: for example, continuous nasogastric or gastrostomy feeds, frequent small amounts of thickened feeds and the addition of complex carbohydrates such as fibre and uncooked corn starch.[4 5] We report on two children treated by a combination of complex carbohydrate and fats to delay gastric emptying and provide a stable release of glucose, leading to normoglycaemia and amelioration of symptoms.

Case reports

CASE 1

At 10 months of age this girl underwent bladder augmentation using gastric mucosa (that is, gastrocystoplasty) for treatment of reflux nephropathy. At 15 months of age she had further bladder augmentation with ileocystoplasty and an antireflux procedure (Nissen's fundoplication) for clinically and radiologically significant gastro-oesophageal reflux. At 17 months (two months after surgery) she was readmitted for evaluation of persisting diarrhoea and food aversion. On specific questioning her parents reported that she also had acute abdominal discomfort and lethargy after meals, accompanied by pallor and sweating.

In hospital, a brief tonic–clonic seizure occurred postprandially. At that time she was found to be hypoglycaemic (1·5 mmol/l) and required correction with a glucose infusion. No other metabolic abnormality was detected. A computed tomographic scan of the brain and an electroencephalogram were both normal. Subsequently, in the hospital, an oral glucose tolerance test (2 g/kg glucose) was performed which showed an initial hyperglycaemic response (blood glucose concentration, 7·8 mmol/l at 30 min) followed by hypoglycaemia (blood glucose 3·5 and 2·1 mmol/l at 45 and 60 min, respectively). Barium swallow showed a normal oesophagus, microgastria, and rapid stomach emptying. The latter was confirmed by a gastric emptying scan with ^{99m}Tc-labelled sulphur colloid which showed no gastric residue at 30 minutes. A diagnosis of dumping syndrome was made and she was placed on frequent small feeds and the addition of corn oil. This alleviated the postprandial glucose abnormalities totally and clinical symptoms partially.

Two months later she was readmitted for continued symptoms relating to the dumping syndrome, including irritability, worsening food aversion, and slow weight gain. She was stabilised with continuous nasogastric feeding (Similac PM 60/40, Ross Laboratories). In an attempt to wean her to bolus feeds during the daytime hours, a safflower oil based fat emulsion (Microlipid 50%, Sherwood Medical Industries) was added to her formula feeds to delay gastric emptying but without any success. Subsequently, uncooked corn starch was added to her formula feeds at a concentration of 50 g/l. Symptoms improved markedly and her blood glucose concentration remained stable throughout the interval between feeds (4·3–5·6 mmol/l). Gradually, nasogastric feedings were changed to three bolus feeds during the day and a 10 hours' overnight continuous infusion. On this regimen her mood improved dramatically, weight increased by 2100 g over the next 140 days, and she began to take small amounts of food by mouth. She is now 23 months old.

CASE 2

This 4 year old boy had a history of accidental ingestion of caustic drain cleaner and subsequent development of strictures in the oesophagus, antrum, glottis, and supraglottis. He underwent a tracheotomy and subsequently a feeding gastrostomy, Nissen's fundoplication, and pyloroplasty. Six months after the operation his mother reported that he was experiencing discomfort during and after gastrostomy bolus feeds. After a clinical diagnosis of delayed gastric emptying he was prescribed metoclopramide. His symptoms worsened considerably and he was admitted to hospital.

He was found to have episodes of tachycardia, sweating, and pallor immediately after feeds. His symptoms were worse after the daytime bolus feeds and he had, by himself, adopted a left lateral position during and after feeds to experience some relief of symptoms. He was clinically diagnosed to have 'intolerance' to feeds and his feeds were diluted to 0·75 strength Isosource (Sandoz Canada), an iso-osmolar, 4·18 kJ (1 kcal)/ml, casein-soy based tube feeding formula. Additional energy was supplied by medium chain triglycerides (MCT Oil, Mead Johnson). This dietary manipulation provided some relief of symptoms.

At this stage he was clinically diagnosed to have dumping syndrome which was confirmed as in the first case. His blood glucose concentration at 30 minutes after a 2 g/kg glucose load was 10·0 mmol/l, which dropped to 2·0 mmol/l at 90 min with marked symptoms. His feeds were changed to 940 ml of Isosource with 90 ml 50% Microlipid, 40 g uncooked corn starch, and 440 ml water, which provided 334·4 kJ/kg/day and 1·8 g/kg/day of protein. The feeds were initially given as three bolus feeds during the day with 12 hour continuous drip at night and subsequently changed to 2 daytime bolus feeds of 375 ml each and nine hour continuous feed at night. This was accompanied by a considerable improvement in postprandial blood glucose and symptoms. The amount of corn starch was increased to 70 g in the feeds (about 50 g/l) which resulted in further resolution of symptoms.

Discussion

These two cases illustrate the occurrence of dumping syndrome after two different gastrointestinal surgical procedures, along with Nissen's fundoplication: that is, gastrocystoplasty and pyloroplasty. Both the patients presented with considerable symptoms and failure to thrive, a major component of which was learned aversion to food as in the study by Hirsig *et al.*[2] In both cases, effective control of symptoms and nutritional rehabilitation was achieved by dietary manipulations alone. Nutritional management was designed in accordance with the underlying altered physiology. Fats were used to delay gastric emptying and uncooked corn starch was used to deliver small amounts of glucose at a steady rate over a relatively longer time period. The latter has been used previously in the management of hypoglycaemia associated with type I glycogen storage disease.[6]

Microlipid was chosen as the fat source for several reasons. Firstly, it is a commercially available fat emulsion that is readily miscible in a liquid phase and thus it is appropriate for use in tube feeding. Secondly, as Microlipid is composed of long chain triglycerides, it will delay the gastric emptying more than medium chain triglycerides. Microlipid also provides a nutritionally balanced fat source with essential fatty acids. The choice of uncooked corn starch was based on several factors: it produces a slow and sustained blood glucose concentration; other commonly used and commercially available glucose polymers (for example, Polycose, Ross Laboratories) have a shorter chain length and produce a sharper and less sustained blood glucose response; corn starch can be used as a bolus and it eliminates the need to use continuous feeding; and finally it is easily available an inexpensive.

The management of dumping syndrome should be aimed at resolving clinical symptoms and improving nutrition simultaneously. This can be effectively achieved by the methods outlined.

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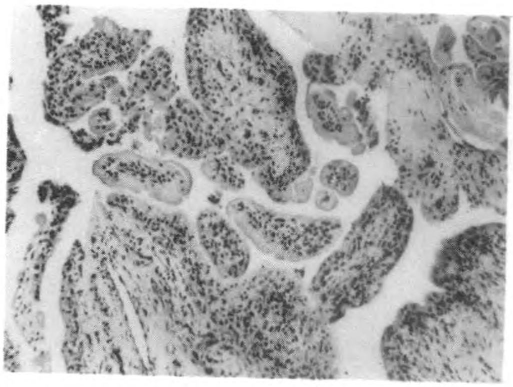
Pigmented villonodular synovitis

Uri Givon, Abraham Ganel, Michael Heim

Abstract

Pigmented villonodular synovitis (PVS) is an uncommon, usually monoarticular disorder encountered mainly in adults. A boy and a girl, both 7 years old, were referred because of recurrent knee effusions. Both were medically treated for other rheumatic disorders for five years. PVS was diagnosed by arthroscopy and synovectomy was curative in both cases.



Biopsy specimen of case 1 showing villous hypertrophy, diffuse histiocytic proliferation, and focal haemosiderin deposition (haemotoxylin and eosin × 100).

Pigmented villonodular synovitis (PVS) comprises a group of idiopathic lesions in joints, tendon sheathes, and bursae. The clinical presentation is of recurrent joint effusions, which can be misdiagnosed as arthritis. Episodes of complete remission may be found between periods of active disease. The histological findings are exuberant synovial proliferation with numerous villi and folds that sometimes fuse into nodules and form locally aggressive intra-articular masses.[1 2] PVS is usually found in young adults and only a few cases were previously reported in children. Because of its rarity diagnosis of PVS in children may be made late. We report two cases of children who were medically treated for suspected rheumatic disorders suffering adverse side effects until the correct diagnosis was made.

Case reports

CASE 1

A previously healthy 2 year old girl started to suffer from recurrent effusions of her left knee. The parents were of Iraqi and Turkish Jewish origin. Juvenile rheumatoid arthritis or familial Mediterranean fever were suspected. Treatment by non-steroidal anti-inflammatory drugs and colchicine was initiated and prednisone and penicillamine were added later. Adverse side effects such as vomiting, diarrhoea, and abdominal pain were encountered, however remissions occurred independently of treatment. The girl was seen in our clinic at the age of 7 years. On examination no abnormalities were found other than in the left knee, which was swollen and warm with limited range of movement. Serological tests and concentrations of antinuclear antibodies were normal; normal results were found on radiography. Arthroscopy demonstrated hypertrophic synovium and defects in the articular cartilage. PVS was diagnosed by a synovial biopsy specimen (figure) and radical synovectomy was curative. Three years later the girl was asymptomatic and no recurrence was found.

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rch Dis Child 1991;**66**:1449–50)

CASE 2

A boy of European Jewish origin had had recurrent right knee effusions since the age of 2 years. He was completely healthy between the spells of the disease. A diagnosis of familial Mediterranean fever had been made and non-steroidal anti-inflammatory drugs and colchicine were prescribed but discontinued because of vomiting and diarrhoea. At the age of 7 years the frequency of attacks increased. On examination the right knee was swollen with limited range of movement. Aspiration yielded serosanguineous fluid. Serological tests and concentrations of antinuclear antibodies were normal; normal results were found on radiography. Arthroscopy demonstrated a large bleeding nodular mass that was excised and on histological examination the diagnosis of PVS was made. The boy was completely healthy one year later without any signs of recurrence.

Discussion

PVS was first described by Jaffe *et al* in 1941.[2] Most of the cases were described in young adults.[1–3] We were able to locate seven reports of PVS in children. Bobechko and Kostuik reported three cases of children with recurrent knee effusions and cutaneous haemangiomas over the involved knees who were found to have PVS.[3] Wendt *et al* reported three generations of the same family who suffered from PVS and multiple lentigines syndrome—a rare skin disease. Two siblings from the third generation had multiple joint involvement.[4] More cases were described in children who had other diseases as well.[5 6] As far as we could ascertain our patients are the first healthy children found to have PVS.

Diagnosis of PVS is usually made late, especially if the afflicted joint is a deep one, such as the hip or shoulder joint.[1] Further delay may be attributed in our cases to the relatively high prevalence of familial Mediterranean fever, a similar joint disorder, in the Israeli population. This disease is hard to rule out and long term medical treatment is indicated in order to prevent late complications.

Treatment of PVS is surgical and 67% of the patients respond well to a radical synovectomy. In 33% of the cases a recurrence was reported and in 22% the result was unsatisfactory. Our patients both had a very good result and returned to normal childhood activities after years of a compromised quality of life.

In conclusion, though rare, PVS occurs in children. Misdiagnosis is associated with prolonged morbidity and various adverse effects of medical treatment. PVS should be considered in the differential diagnosis of recurrent joint effusion in children. Early arthroscopy should perhaps be considered in cases of pauciarticular arthritis when antinuclear antibodies are not present.

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Archives of Disease in Childhood 1991; **66:** 1451–1453

HISTORIAL REVIEW

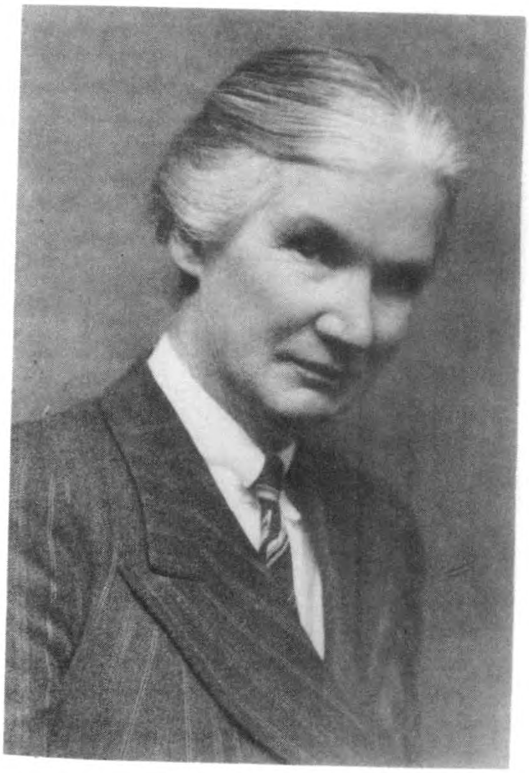
Helen Mackay and anaemia in infancy—then and now

David Stevens

Born in Inverness in 1891, with both of her parents from Highland families, Helen Marion Macpherson Mackay had strong Scottish roots, but it was also possible to recognise her as a product of her school, Cheltenham Ladies College. She went on to study medicine at the Royal Free Hospital and qualified in 1914. She decided to become a paediatrician and after completing some posts in London went to Vienna at the end of the first world war to study rickets under the guidance of Professor Pirquet at the University Kinderklinik.

Rickets was common in young infants in Vienna but she was surprised to find that anaemia was almost universal and became interested in finding the cause. It was recognised that anaemia was common in infants who were given artificial feeds but the reason was not clear. Anaemia and rickets were often found together and some paediatricians thought that they might have a common cause. Part of her work in the 1920s was to show that light therapy, which was very much in vogue at the time, had no effect on anaemia. It was known that iron deficiency was a cause of anaemia in infancy but there were no soundly based studies on the epidemiology and the prevalence of anaemia in infancy, no reliable figures for normal haemoglobin concentrations in infancy, and therefore no agreement on the definition of anaemia in this age group. So it was against this background that Helen Mackay's work took place. Having shown that many of the anaemic infants in Vienna responded to iron, she came back to London to work at the Queen's Hospital, later to be called the Queen Elizabeth Hospital, and made more systematic studies on anaemia in infancy.

Helen Mackay worked as a consultant paediatrician in the east end of London until her retirement in 1959; she died in 1965. She recognised the impact of social conditions on child health and carried this conviction into her working life by setting up clinics for mothers and babies in the community. Her clinical work at the Queen's Hospital, the Mother's Hospital, and in the community was inevitably centred on the disadvantaged and her research essentially an extension of this work. Dressed in the familiar brown suit she wore every day, with her remarkable memory, complete commitment to the care of young children, and insistence on the highest standards of clinical note keeping, Helen Mackay created an indelible impression on all who worked with her and was held in awe as well as affection by the staff of the Queen's Hospital. She was by nature reserved and formal, rarely indulged in small talk, and belonged to an age when colleagues were seldom addressed by their Christian names. In her own home she and her companion, Miss Lorel Goodfellow, showed that formality and affection could go together by invariably calling each other 'Mackay' and 'Goodfellow'! Her infrequent holidays were usually taken in Scotland or on the moors where she liked to walk and enjoy ornithology.



Helen Mackay had many honours bestowed on her in recognition of her work as a paediatrician and for her research contributions into anaemia and infant nutrition. Two of her achievements demonstrate her importance in British paediatrics and at the same time remind us of the belated entry of women into the male bastions of medicine: in 1934 she became the

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This article is an expanded version of 'Helen Mackay, another iron lady' that appeared in the *BMJ* on 20 July 1991;**303:**147–8.

first woman fellow of the Royal College of Physicians and in 1945 was one of the first women to be elected to the British Paediatric Association. One hundred years after her birth, new work on the untoward effects of iron deficiency on young children has drawn us again to the importance of her research, the soundness of which is demonstrated by how little her conclusions need to be altered in the light of our knowledge today. Respected clinician, a pioneer who brought paediatric care into the community, and unforgettable personality: these are some of the memories of those who knew her, but to generations of paediatricians to come Helen Mackay will be remembered for laying down the foundations of our knowledge of iron deficiency anaemia in infancy.

Prevalence and cause of anaemia in infancy

In the east end of London in the 1920s the prevalence and severity of iron deficiency in infancy were similar to that in the most deprived areas of the developing world today. Without iron treatment the haemoglobin concentrations of more than 90% of infants failed to reach 80% (approximately 110 g/l) at any time between 6 months and 2 years of age,[1-3] whereas 81% of those who took iron regularly achieved haemoglobin concentrations above this level. How much change has there been since the 1920s? In 1971, David Burman reported that infants in Bristol who were not given iron supplements had similar haemoglobin concentrations to those who were given iron in Helen Mackay's study.[4] He showed that routine iron supplementation for infants was not justified in present day Britain. However, when disadvantaged groups are examined separately the position is not quite so good.[5] Iron deficiency anaemia is still common in infants in inner city areas and in one study 18% of the white and 26% of Asian infants were found to have iron deficiency anaemia.[6] Helen Mackay recorded the family income and social conditions of the infants in her study but was unable to compare systematically the prevalence of iron deficiency in infants from different backgrounds. One such study in the USA showed that the prevalence of iron deficiency and anaemia in young infants was three times greater in poor compared with more affluent groups of society but this difference became much less noticeable after 3 years of age.[7]

Diet and iron deficiency

Infants in the 1920s were weaned late and iron fortified infant feeds were not available. Breast feeding was continued much longer than is the practice in the developed world today and artificial feeds consisted of reconstituted powdered cows' milk, sometimes with added carbohydrate, but with no added iron or vitamins. Solid feeds play an important part in the prevention of iron deficiency but Helen Mackay shared with today's investigators the difficulty of making an accurate assessment of the impact of different types of solid feeds on iron deficiency in infancy. Her most important dietary finding was to show that haemoglobin concentrations were higher in breast fed infants throughout most of infancy. Modern studies have confirmed that breast fed babies are more likely to maintain normal serum ferritin concentrations in the first six to nine months of life than those fed with unmodified cows' milk.[8] The disadvantage of giving unmodified cows' milk in the first year of life was confirmed in a study in which haemoglobin and serum ferritin concentrations were found to be lower in infants fed with unmodified cows' milk compared with those who were fed with an iron supplemented formula milk.[9]

'The percentage of iron retained is apparently less in a baby fed on cows' milk . . . than one fed on human milk'.[10] Helen Mackay correctly identified the most important reason for the better iron status in breast fed infants. About 50% of the iron in breast milk is absorbed compared with about 10% in cows' milk.[11] Most of the modern infant formulas contain added iron to compensate for poor absorption. About one third of infants fed with 'doorstep' cows' milk have been shown to loose blood in the stools, which may contribute to the risk of iron deficiency.[12]

Low birth weight and iron deficiency

Helen Mackay showed that the initial drop of haemoglobin as well as the degree of anaemia after six months was more profound in low birthweight infants. This second drop can be prevented by iron supplementation,[13] which should be given to low birthweight infants after 1 month of age whereas the initial fall has a nadir at 6–8 weeks of age and is not due to any nutritional deficiency. Helen Mackay correctly attributed the increased risk of iron deficiency to low stores of iron at birth in low birthweight infants and to the demands of growth.

Non-haematological effects of iron deficiency

Helen Mackay found that infants who were given iron supplements had fewer documented infections, gained more weight, and were noticeably more healthy than those who were not given iron. The existence or otherwise of harmful non-haematological effects of iron deficiency has undoubtedly been the most controversial aspect of iron deficiency over the last 60 years. Until recently the sceptics seemed to hold sway but over the last 10 years there has been an impressive group of studies showing that treatment of iron deficiency improves the development and growth of young children and makes them happier.[14] The effect of iron treatment on the risk of infection is still a matter of debate[15] with the evidence suggesting that it may reduce the risk of infection or have no effect in non-malarial areas and possibly increase the risk in some malarial parts of the world.

Normal haemoglobin in infancy and the diagnosis of iron deficiency anaemia

'The normal haemoglobin percentage in the blood in infancy from four months upwards is at least 80%'[1] (approximately 110 g/l[3]). Helen Mackay was the first person to try to define the lower limit of normal haemoglobin throughout infancy by examining a group of children who had been supplemented with iron. Her definition of anaemia in this age group closely resembles that accepted by the World Health Organisation 40 years later.[16] In her own hospital she encouraged her staff to give an iron sulphate preparation, affectionately known as 'Mist Helen Mackay', to all children suspected of having iron deficiency anaemia. Since that time tests such as serum ferritin and transferrin saturation have been introduced to help with the diagnosis of iron deficiency but a trial of iron treatment remains the 'gold standard' test of iron deficiency anaemia in infancy.

I am grateful to Dr BD Corner, Dr MJ Wilmers, Dr ADM Jackson, Mr Valentine Swain, and Professor R Bouden for invaluable help in the preparation of this manuscript.

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PERSONAL PRACTICE

Management of intractable epilepsy

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Intractable epilepsy is a common problem confronting the paediatrician. Although there is little epidemiological data available, it is estimated that 10 to 20% of childhood epilepsies are intractable.[1]

Intractability here is taken to mean epilepsy that is not controlled after an adequate (see below) trial of first line conventional antiepileptic drugs treatment, singly and in combination. It is not the frequency of seizures as such that defines them as intractable, but rather their resistance to control by treatment.

When confronted with a child with apparently intractable epilepsy, three questions need to be considered: (1) Does the patient have epilepsy? (2) What is the underlying cause/diagnosis? (3) Is the epilepsy truly intractable?

(1) Does the patient have epilepsy

It is estimated that 20 to 30% of patients referred for management of intractable epilepsy do not have epilepsy.[2 3] In the assessment of paraoxysmal disorders the most important aspect is the history. This history needs to be from both the patient and one or more eye witnesses.

The largest group of disorders mistaken for epilepsy are the various forms of anoxic seizures or syncopal attacks. This has been comprehensively discussed by Stephenson in his recent monograph.[4] Migraine is another important group with a complex inter-relationship with epilepsy. There are a large number of less common non-epileptic paroxysmal disorders in childhood[5] and it behoves the clinician who deals with epilepsy to be familiar with them. There are also undoubtedly some disorders that are incompletely understood that are difficult to classify as epileptic or otherwise. Psychic seizures and pseudoseizures are another important group. It should be remembered that pseudoseizures are more common in patients with epilepsy than in those without.

Complementary information is given by the electroencephalogram (EEG). Paroxysmal activity on the EEG does not mean that a patient's attacks are necessarily epileptic in nature. Recording a seizure during an EEG is extremely helpful. In cases with very frequent attacks, long term monitoring with a video EEG and polygraphy may help resolve the issue.

If there is persistent doubt about the diagnosis then it is better to wait and see before starting treatment. If the patient is already on treatment the antiepileptic drugs can be gradually reduced and the effects observed.

(2) What is the underlying cause/diagnosis?

In some cases the cause is obvious, for example asphyxial brain damage, congenital infection, or cerebral malformation. However, in many cases this is not so and there is always the question of whether there is an underlying neurodegenerative disease.

All cases of intractable epilepsy should have a high resolution computed tomography, and ideally, magnetic resonance imaging performed. With these imaging techniques an increasing number of neuronal migration disorders, focal or generalised, are being detected.[6] A follow up computed tomogram should also be carried out after three to four years if the cause is in doubt, particularly in cases where there is clearly a focal EEG abnormality or seizure pattern. In this way very slow growing tumours, such as oligodendrogliomas, may be detected.

Although there are a large number of neurometabolic diseases in which seizures are prominent, most of these will be suggested by other clinical features. There are, however, a few conditions in which intractable epilepsy may be the most prominent initial feature, and in which the other clinical features may be difficult to detect against the background of intractable epilepsy (table). Pyridoxine dependency should always be excluded, particularly in infantile epilepsy.[7]

As well as a diagnosis of specific disease entities it is also important to try and make a diagnosis of the type of epilepsy or epileptic syndrome,[8 9] as this helps in giving a prognosis, choice of treatment, and in research.

(3) Is the epilepsy truly intractable?

Epilepsy is often labelled 'intractable' when it is not. There are several causes of such 'pseudo-intractable epilepsy'.[10] When reviewing the history of previous treatments it is necessary to document the following for each antiepileptic drug: the duration of treatment, dose/kg, clinical effects, side effects, and blood concentrations (where appropriate). If a drug has been stopped

Progressive diseases which may present with intractable epilepsy before other clinical features are prominent

Age of onset	*Disease*
Neonate	Non-ketotic hyperglycinaemia
	Molybdenum cofactor deficiency
	Menkes' disease
	Late infantile neuronal ceroid lipofuscinosis
	Progressive neuronal degeneration of childhood
↓	Huntington's disease
Teenage	Progressive myoclonus epilepsy syndromes[24]

after a very short time the reason for changing it needs to be determined. When such a drug history is available it should be clear whether there has been an adequate trial of each drug, alone or in combination. Given the spontaneously fluctuating nature of most epilepsies, each trial of drugs or combination should be given for a minimum of one month (unless there is an acute severe deterioration). For this reason it is normally preferable that drug changes occur at home and are monitored in outpatients rather than in hospital. This has the added benefit of preventing doctors succumbing to the seemingly irresistable temptation to change antiepileptic drugs every few days in a hospitalised child with uncontrolled seizures. It is also important to decide whether an adequate dose of each drug has been given. In this respect the concept of a 'therapeutic range' of blood concentrations of antiepileptic drugs is not particularly helpful. This is particularly so for sodium valproate and carbamazepine. (If a patient with intractable epilepsy on sodium valproate or carbamazepine has no apparent side effects, then these can be reasonably increased despite a blood concentration in the so called therapeutic range.) Persistently low blood concentrations may however, indicate non-compliance, which is an important cause of poor seizure control.[11]

A drug history such as this may reveal that an insufficient trial of one or more drugs may have been given and in some patients going back to an antiepileptic drug that has previously been tried in a different dose or combination is sufficient to control the seizures. The possibility that the treatment is making the epilepsy worse must always be considered. It is probable that all the commonly used antiepileptic drugs can at some time or other aggravate seizures.

In someone with continuous seizures there is no justification for polytherapy. Occasionally seizures will improve on decreasing or stopping drugs,[12] more often however, the seizures remain the same, but alertness and coordination improve.

The benzodiazepines warrant special mention because of their often dramatic effect in improving seizures. They are, however, a very frustrating group of drugs in that tolerance to their effects develop in at least two thirds of cases. In addition side effects are often considerable (cognitive impairment, behavioural disturbance). Clobazam probably results in fewer behavioural side effects than the other benzodiazepines. There are, however, some patients who respond well to benzodiazepines without side effects and do not develop tolerance. Another difficulty with the benzodiazepines is the occurrence of withdrawal seizures on decreasing the dose. This is often done too fast resulting in reluctance on the part of the parents to try again. Benzodiazepines should be decreased very slowly in small steps, no faster than every two to four weeks.

Surgical treatment

Any patients with intractable epilepsy should be considered as a possible candidate for surgical treatment. The indications for surgical treatment are being increasingly refined[13] as it is clear that outcome is critically dependent on selection criteria. Surgery is most likely to be of benefit for intractable partial epilepsy, the best results being from series of temporal lobectomies carried out for complex partial seizures.[14] Extratemporal resection may be of benefit. In patients with a hemiplegia and intractable epilepsy arising from an abnormal hemisphere, hemispherectomy may be dramatically beneficial.[15] Section of the corpus callosum (partial or complete) has been recommended for patients with intractable drop attacks and other generalised seizures. Adverse affects are few but some patients have become worse. The exact place of this procedure has not yet been determined.[16] Even if the underlying cause of the epilepsy is a generalised disorder such as tuberous sclerosis consideration should be given to surgical treatment if the seizures appear to arise from one particular area.

It is beyond the scope of this article to discuss in detail all aspects of surgical treatment of the epilepsy. It is clear, however, that surgical treatment should be considered earlier than has usually been the case.

Having established that the child has true intractable epilepsy and that surgery is not likely to be of benefit an attempt should be made to reduce antiepileptic drug treatment to the minimum that controls unacceptable seizures. This is necessarily vague as what is acceptable for the child, family, doctor, or school will vary from patient to patient. If a child has occasional prolonged seizures only, that cannot be prevented by continuous treatment it may be more appropriate to discontinue regular treatment and for the parents to keep a supply of rectal diazepam or paraldehyde to use in the event of such a seizure. It is often helpful to determine what is the most troublesome type of attack and maintain the child on the drugs that appeared to help this seizure the most.

Having decreased conventional antiepileptic drug treatment to a minimum, consideration needs to be given to other types of treatment. It is not the purpose of this article to list all the agents that have been tried in intractable epilepsy. One of the reasons why it is unclear whether such treatments work or not is because they are rarely used in a systematic or controlled way with outcomes adequately defined or documented. The lack of adequate studies makes interpreting the reported efficacy of each of the following treatments difficult if not impossible. Although such evaluation is time consuming and complex, it is essential in order to interpret the effects of a new treatment.

Dietary treatment

The ketogenic diet may be successful in controlling seizures, particularly in young children.[17] The various different diets all appear to be effective.

Food allergy as a cause or contributor to epilepsy has been proposed recently. A trial of the so called 'oligoantigenic' or few foods diet showed improvement in seizures in 50% of the children studied. The responders were children who had symptoms of migraine as well as epilepsy.[18] The placebo effect of such diets is very strong, however, and although enormously complex to design and interpret, further studies are needed.

Steroids

Claims have been made for the efficacy of steroids in Landau-Kleffner syndrome, nonconvulsive status epilepticus, and the syndrome of electrical status epilepticus of sleep. Though individual patients undoubtedly may respond, with the possible exception of some cases of Landau-Kleffner syndrome, there is currently no clear indication for long term steroid treatment in intractable epilepsy.

Immunoglobulins

Immunoglobulins have been used in the treatment of intractable epilepsy for a number of years. Most, but not all, studies have reported benefit.[19] Several studies have suggested that those with selective IgG_2 deficiency are more likely to respond and some long term responses have been described.[20] The optimal dose has not yet been determined. Although expensive, immunoglobulins are safe and warrant further study.

New antiepileptic drugs

There are at the moment at least 10 new antiepileptic drugs undergoing clinical evaluation and others at the preclinical evaluation stage. Vigabatrin has recently become available for general use and appears particularly useful against partial seizures. It may also be effective in the treatment of infantile spasms, but it appears less successful against other types of intractable epilepsy in childhood.[21 22]

Lamotrigine is likely to become available in the next few years for general use. Its role is not yet clear, but it has been of benefit in some studies (SJ Wallace, abstract presented at British Paediatric Neurology Association (BPNA) 1989, J Gibbs *et al*, abstract presented at BPNA 1991).

Non-pharmacological treatment

In all cases of epilepsy, whether intractable or not, an exhaustive search should be made for precipitating or aggravating factors. This may reveal that the epilepsy is a reflex epilepsy and can be treated by avoiding the precipitating stimulus, with or without antiepileptic drugs.[23] In intractable epilepsy that is not reflex there may none the less be factors internal or external that precipitate or aggravate seizures. This has led to attempted behavioural treatments of epilepsy, either by biofeedback methods or using relaxation techniques.[11] This is most likely to be of value when there is an obvious warning before the seizure occurring, or when tension and anxiety seems to aggravate seizure frequency. Research is needed to evaluate these techniques in younger children and those with more severe cognitive impairment.

The social, emotional, and educational effects of intractable epilepsy on the child and the functioning of the family are often devastating. Because of the fluctuating nature of epilepsy, it is very difficult for any sort of normal adjustment process to loss or disease to occur. When the epilepsy is clearly intractable it is important that the parents are told this and helped to understand it. The goals of treatment need to be redefined. At the same time this must be balanced with keeping some hope alive. This is both necessary and justifiable. Schooling is often extremely difficult and children may be unable to be accommodated even in special schools. This is one situation where there is a real place for residential schools for children with epilepsy. Once in such an environment the stigma of having epilepsy will often evaporate and the child may improve significantly.

Future research should be directed towards the development of new drugs, the development of surgical treatments, towards developing better ways of analysing the response to antiepileptic drugs, and for quantifying seizure frequency more accurately.

It is to be hoped that in the 'decade of the brain' new insights into the basic mechanism of intractable epilepsy will be gained that will ultimately lead to better treatments.

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STATISTICS FROM THE INSIDE

2. Significance tests

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To many people, significance testing is the be-all and end-all of statistical analysis and expertise in statistics is synonymous with the ability to choose a significance test suitable for a particular problem. Nothing could be further from the truth. The level of significance of a body of data (let alone the mere fact that this level does or does not surpass an arbitrary limit) at best conveys only a part of the information that the data contain, and in many problems the assessment of significance is simply a waste of time. For all this, significance testing plays such a major part in most elementary statistical teaching that it is of great importance to come to terms with the rather tricky concepts that are involved.

The argument involved in significance testing closely follows the popperian approach to scientific reasoning, though its use predates Popper's work by a considerable period. In the briefest of summaries, Popper asserts that science progresses through a sequence of conjectures and refutations. First a conjectural hypothesis is put forward to explain the situation in some branch of science. Data are then collected and the scientist decides whether these are of such a kind as to refute the conjecture. If this is so, a fresh conjecture must be made; if not, then further data, perhaps of a different kind, are required.

Suppose then that we administer a new treatment and a placebo control in random order to a number of asthma patients, measure the forced vital capacities under each condition and form the difference (treatment−control) for each of the patients. Statistically speaking, we can envisage the data as coming from a population of patients with a variate* given by the difference in forced vital capacity between the two conditions. A question we might wish to answer is 'Does the mean of the population—the average effect of the treatment over and above that of the control—differ from zero?' The *sample* average is almost certainly not equal to zero, but this may be a chance effect in the sense that, if we took further samples from the same population, we might get sample averages which were as likely to be positive as negative. How plausible is such a situation in the light of the data we have obtained?

Make the provisional conjecture that the population average difference is truly equal to zero—this conjecture is known as the *null hypothesis*. It is now possible, perhaps making further assumptions about the distribution of differences in the population, to calculate mathematically the probability of obtaining a sample mean as large as or greater than the one actually observed. This probability is the *significance level* of the data in relation to the question at issue.

Suppose next that the significance level is very small, say 0·001 or 1 in 1000. There are two possible explanations for this. Either: (a) something very improbable has happened or (b) the null hypothesis is false.

It is natural to accept the second of these and to assert that, in the light of the data, the average difference in the population is not equal to zero. Obviously this assertion may be mistaken, but if it is we have observed the sort of data which would only occur once per 1000 samples in the long run.

If on the other hand the significance level is quite large, 0·40 say, we can no longer choose alternative (b) with any confidence. The data are of a kind which would arise quite commonly if the null hypothesis were true; we are not in a position to disprove it, even provisionally. Notice that we are not in a position to accept it, to say with any certainty that the null hypothesis is true—many other hypotheses will be consistent with our data. We are at best in a 'not proven' situation.

A result which has a small significance probability is often said to be statistically *significant*. Two remarks are immediately called for. First, the word 'significant' is used as a technical term and has nothing whatever to do with its standard dictionary meaning of 'important'. The significance testing argument as outlined above says nothing at all about the actual size of the population mean. In statistical jargon, 'significant' is roughly equivalent to 'consistent' or more roughly still, and with several reservations, to 'probably real'. It is good practice to make these translations when reading the results of a statistical analysis—it shows up nonsense phrases like 'almost significant' or 'probably significant'. On the same lines, the opposite of 'significant' is 'non-significant', never 'insignificant'.

The second issue is where to draw the line between 'significant' and 'non-significant'. No such line exists and any distinction of this kind is completely arbitrary. A convention has grown up which places the dividing line at a significance level of 0·05. The only merit of this choice is that it relates closely to a deviation in a Normal

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*A variate is an attribute—here the numerical value of the difference—associated with each member of a population; see the first article of this series (*Arch Dis Child* 1991;**66:**1355–6).

distribution equal to two standard deviations, and thus lends itself readily to mental arithmetic. The convention is harmless only if the temptation can be resisted of assuming that results with a significance level of 0·04 can be regarded as firmly established, whereas those with a significance level of 0·06 can be labelled NS and totally ignored. Some authors do not even report such findings numerically, a most pernicious practice. It is usually far better to quote actual significance levels, whatever their size.

When one of the two possible assertions (a) and (b) listed above is made, it may of course be mistaken. Two types of error can thus be distinguished. We may assert that a null hypothesis is false (that a non-zero population mean difference exists) when in fact it is true (the actual population mean difference is equal to zero). This is a false positive and is called an error of type I. Equally, and at least as importantly, we may fail to assert the falsity of a null hypothesis which is false in reality—we fail to establish the existence of a non-zero population mean difference when one actually exists. This is a sort of false negative and is called an error of type II.

The two types of error and their probabilities of occurrence can be used to throw light upon the difficult statistical question 'How large should my study be?' Suppose that, when planning a study, we decide that we can tolerate a type I error probability no larger than some small quantity α. This means that we shall consider a true non-zero mean difference as being established by our data if the significance level when we obtain them is less than or equal to α. Let us also select some non-zero value x of the population mean difference that we are anxious not to overlook. If the true difference is as big as x we would like the probability of a type II error (failing to achieve a result significant at level α) to be less than some small quantity β. The quantities α and $(1\text{-}\beta)$ are called the *size* and the *power* of the contemplated test (note that the power depends upon the choice of the value x). With the aid of subsidiary assumptions of Normality, etc, it is then possible to calculate the required number of subjects in the study. Given this number, one can (and should) also make a plot of the *power curve* which relates $(1\text{-}\beta)$ to x and shows the probability of establishing as significant at level α a difference of any particular size. Notice that the concepts of size and power are of interest at the planning stage of a study and before the data have been acquired. At the end of the study, a suitable analysis of the data can show the significance level actually achieved and also what values x are 'reasonably consistent' with the data in a sense to be described in a subsequent note.

The selection of a significance test which is appropriate to a particular set of data is a problem with two aspects. Firstly, the test must take proper account of the way the data were collected and the resulting pattern of dependencies between them. If the data collection has involved some kind of pairing or matching of observations, this should be allowed for in the statistical model for the data that underlies the test. Secondly, different tests may make different assumptions—for example, some tests for continuous data assume Normal distributions while others (known as 'distribution-free' or 'non-parametric') avoid this assumption. The choice between competing tests is not entirely straightforward and I hope to return to the subject in a later article.

Finally, let us return to the basic question that underlies any significance test, 'Does the population quantity of interest (for example, the population mean) *differ from* zero?'. In most applications it is appropriate to add the words 'in either direction' at the end of the question, so that we ask, for instance, 'Is the treatment *different from* the placebo in its effect on forced vital capacity?' It is sometimes tempting to specialise the question to indicate one direction only—'Is the mean (treatment – placebo) difference in forced vital capacity *greater than* zero?', that is, 'Is the treatment *better* than the placebo?' for example. This question leads to a *one tailed* significance test. Typically the significance level of a particular sample result is only half that of the more usual two tailed test so that a more significant result is obtained.

The possible use of a one tailed test is of theoretical interest because it opens up the idea of the *plausibility* of different hypotheses—essentially it says that hypothetical departures from the null situation in the 'wrong' direction are so implausible that they can be ignored. Once such an idea is accepted it is a short step to querying the plausibility of the null hypothesis itself. In many studies, is it really plausible that the effect of a new treatment is *exactly* equal to that of a control (note that 'roughly equal' or even 'closely equal' will not do at all)? Such a question not only casts doubt upon the usefulness of significance testing as such, but also points towards the quite different bayesian or subjectivist approach to statistical analysis, where the data are used to modify the subjective probabilities of the researcher or reader. This is currently the subject of brisk controversy among statisticians.

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CURRENT TOPIC

Adolescent psychoses: treatment and service provision

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The generic term 'psychosis' is enduring but imprecise and the traditional division between neurosis and psychosis will be discouraged in the 10th revision of the *International Classification of Diseases* (ICD-10), to be published in 1992.[1] However, it is used in ICD-9[2] and in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III-R).[3] It still has an established place in psychiatric parlance, indicating the presence of hallucinations, delusions or certain types of abnormal behaviour, namely, gross excitement and over-activity; severe, prolonged, social withdrawal; marked psychomotor retardation and catatonic behaviour. Its use does not imply either greater severity, although this is often the case, or impairment of insight or reality testing. With these reservations, it is permissible to refer to a group of adolescent psychoses. Categories of psychoses in ICD-9 include those with origin specific to childhood, principally infantile autism, but this condition is viewed currently as a pervasive developmental disorder and no longer a form of childhood psychosis. This review is concerned chiefly with schizophrenia, schizotypal disorders, drug induced psychoses, and affective disorders arising in adolescence.

There is no unique adolescent psychosis and the view that 'adolescent turmoil' represents a 'normal psychosis' is outdated.[4] Instead, adolescent disorders need to be seen in the context of all psychoses occurring in children and adults, and it is generally accepted that adult diagnostic criteria are applicable. Nevertheless, adolescence has a pathoplastic influence, giving disorders staged characteristics and colouring the content of psychotic symptomatology, sometimes making recognition difficult.

Morbidity surveys suggest that the one year prevalence of psychosis in mid-adolescence is less than one per thousand.[5] The proportion of psychotic patients in adolescent outpatient clinics is commonly about 5% of referrals[6] and reported figures for inpatients vary from 2% to over 22%. About 3% of all psychiatric first admissions for children aged 10–14 years are for psychoses, but the figure rises to 21% for those aged 15–19 years.[7]

The psychoses occupy a neglected place in adolescent medicine and psychiatry. Services for psychotic adolescents are not well developed and academic interest has been limited. This is explained partly by the fact that the prominent interests of staff drawn to work with adolescents are in maturational, social, and family processes. Disorders construed in terms of disturbance of these processes suit multidisciplinary team consensus, as the emergent treatments are interdisciplinary, for example, family therapy. Psychotic disorders, traditionally the prerogative of doctors and nurses, however, have not fitted readily into this social dynamic model. The unknown aetiology, with genetic and possible organic factors, precludes developmental or psychodynamic explanations and pharmacotherapy tends to exclude non-medical staff. Interest in psychosis may be diluted also if staff have little or no formal psychiatric training or experience of adult disorders, because the incomprehensibility of psychosis can be alienating.

Aetiology

The psychoses comprise a disparate group of disorders and there is no single aetiological pattern. There are well established genetic factors in schizophrenia and the affective disorders. While there may be childhood precursors of adult schizophrenia, these are not sufficiently specific to enable early detection. Some psychotic reactions may be symptomatic of organic disorders, but neurological and biochemical leads in schizophrenia and the affective disorders have so far proved inconclusive. Stressful life events often play a part in precipitating disorders and exposure to high levels of emotion in the family promotes relapse in schizophrenia. Despite much speculation, there is no enduring evidence for the causative importance of abnormal family processes, although family factors may play a part in either maintaining or abbreviating psychotic episodes.

Diagnosis

Presenting problems are likely to be very varied, including violence, destructive outbursts, bizarre behaviour, delusional states, suicide attempts, excitement, disinhibited sexual behaviour, and repeated absconding. As psychotic symptomatology displays such diversity, careful syndromal diagnosis is essential for clinical management, because of the different treatment strategies that may be indicated. A key task is disentangling maturational features, such as emotional lability and ordinary adolescent concerns, from psychopathological phenomena. Adolescents with severe disturbance of emotional and personality development (borderline disorders) are hard to understand and may appear incoherent, but very few have psychotic disorders.[8] It is characteristic of the adolescent psychoses, however, that precise diagnosis may be difficult and lengthy observation and assessment may be necessary. This applies particularly to distinguishing between first episodes of schizophrenia and mania, but such difficulty should encourage clinicians to be as rigorous as possible in diagnosis and not simply to resort to the unqualified use of the term adolescent psychosis. In all cases, possible organic causes of psychosis, including rare neurodegenerative conditions, need to be investigated. Clarification of the psychiatric syndrome only forms one part of the full diagnostic formulation, which comprises consideration of specific developmental delays, intellectual level, medical conditions, and abnormal psychosocial situations.

Identification of organic psychosis due, for example, to toxic states, is likely to be clear cut, although the precise causation can be obscure. However, differential diagnosis can be difficult when there is the possibility of organic brain disease. For example, the early signs of subacute sclerosing panencephalitis may resemble schizophrenia, until progressive dementia, with myoclonus and epilepsy, supervenes. Seizure disorder, especially when there is temporal lobe involvement, can be associated with schizophrenia-like psychosis, and anticonvulsants themselves can also produce psychotic states. Drug induced disorders will be influenced by the substance involved, for example, cocaine, hallucinogens, or cannabis, and are characterised usually by hallucinations, delusions, misidentifications, psychomotor disturbance, and abnormal affect. Occasionally, hallucinations can be induced by prescribed drugs (for example, methylphenidate, promethazine hydrochloride, and pseudoephedrine). Schizophrenia is rare in childhood and knowledge regarding it remains limited.[9–11] Incidence increases after puberty and the usual age of onset is 15 to 45 years. In the initial clinical picture of adolescent schizophrenia, Schneider's first rank symptoms may be fleeting, difficult to elicit, or absent.[12] The common presentation is the acute syndrome, with falling off in social and academic performance, mood disturbance, incoherent speech, bizarre actions, hallucinations, delusions, and preoccupation with inner thoughts. Diagnostic problems arise if there are affective features, insidious deterioration of personality, or evidence of clouding of consciousness and perplexity. It is not uncommon for apparently affective disorders to declare themselves eventually as schizophrenic. Paranoid states, without typical schizophrenic features, are unusual in adolescents. Reactive (psychogenic) psychoses, attributable largely or entirely to stressful experiences may occur, but distinction from schizophrenia is uncertain. They are often transient and appear more likely to occur in teenagers from ethnic minorities.

Affective psychoses, characterised by mood swings to depression or elation, and cyclothymic symptoms are rare before puberty, but gradually increase in incidence during adolescence to reach adult levels. Although depressive features are common in adolescence, recognition of affective psychoses, resembling adult 'endogenous' syndromes, may be hampered by developmental differences in symptomatology.[13 14] Depression in adolescents is influenced by environment more readily than in adults; lowering of mood is less fixed and features like self depreciation are infrequent. Suicide is very rare before puberty, but incidence increases during adolescence. First episodes of adolescent mania may be misdiagnosed as schizophrenia[15] unless classic features are present but, after several relapses, a recurrent or cyclical pattern may emerge. There is a risk of misinterpreting symptoms like euphoria and being misled by potential psychogenic factors, which may mask and aggravate, but not necessarily cause, affective disorders.

Treatment

SERVICE PROVISION

Although the number of psychotic adolescents is small, they can make disproportionate demands on staff and resources. The service requirements are clear. Psychiatric outpatient and liaison services must be able to respond promptly to urgent referrals and there needs to be an accessible inpatient adolescent unit with emergency beds and a flexible admission policy so that, if required, hospitalisation can occur without delay. The unit milieu needs to be such that psychotic patients are not excluded and that it is conducive to eclectic treatment. Skilled, adaptable nursing is required, on a 24 hour basis, seven days a week. When adolescents present with possible psychotic states in paediatric or general medical settings, early involvement of an adolescent psychiatrist is desirable, for diagnostic assessment and assistance in management, especially if continuing medical investigation is indicated. This also facilitates subsequent transfer to a psychiatric unit if necessary.

Despite the proliferation of psychiatric adolescent units since the late 1960s there are still significant deficiencies.[16] The Health Advisory Service found recently that clinical services were variable and incomplete,[17] especially for acutely disturbed adolescents, emergencies, rehabilitation, and long term care. Treatment of psychotic teenagers may still occur in adult mental hospital wards and, although this need not be wholly adverse, the adolescent is likely to miss, at least, social and educational activities with peers. The optimum admission policy for adolescent units is controversial, the main distinction being between general purpose units, catering for a wide range of patients, and those concentrating on specific diagnostic groups or specialised therapeutic approaches, the latter models running the risk of excluding the psychoses.

INITIAL TREATMENT

The optimum management of psychotic

adolescents calls for the earliest possible identification and diagnosis, although many child and adolescent psychiatrists are reticent about the implications of identifying severe, potentially life long disorders like schizophrenia in children and teenagers. Treatment will be concerned with a wider range of problems and handicaps than the psychotic process and intervention has to be tailored pragmatically to the symptomatology and needs of individual teenagers and their families.

Although the overall aim is to use outpatient or day hospital care as far as possible, hospital admission is commonly advisable, often after an emergency referral. Parental authority for admission is required for children under 16 years and, occasionally, compulsory admission under the Mental Health Act 1983, or the Mental Health (Scotland) Act 1984, is needed. The intention should be to employ hospitalisation only during the acute phase of the disorder, while assessment and diagnosis are undertaken, treatment initiated, plans for rehabilitation and aftercare are being established, and the coping capacity of parents and others involved in management is restored or enhanced.

Individual psychiatric treatment needs to be based on straightforward communication and counselling about day to day maturational, social, and educational problems. It should be supportive and non-confrontational and, for these reasons, exposure to stressful group therapy is inappropriate. There are few indications for psychoanalytic psychotherapy. There is always an important role for family work, aimed at providing candid information and support, reducing high expressed emotion in the families of schizophrenics and, in all cases, encouraging realistic expectations, the acceptance of relapses, and the possibility of long term disabilities.[18]

Pharmacotherapy is essential in most adolescent onset psychoses. Treatment with phenothiazines (for example, chlorpromazine), thioxanthenes (for example, flupenthixol), or butyrophenones (for example, haloperidol) is the mainstay in acute and chronic schizophrenia and schizotypal disorders. Depot preparations are particularly useful for maintenance treatment in adolescents who are unreliable in taking oral medication. Heterocyclic antidepressants and newer unrelated preparations, such as fluoxetine, can be used in adolescent depression, but there is limited information about their efficacy and documented recommendations are not available.[19] Occasional prophylactic use is made of lithium carbonate.[20] Electroconvulsive therapy is rarely necessary with adolescents, but may be indicated in severe protracted depression.

There is considerable scope for *behavioural modification*, particularly in reducing withdrawn or socially unacceptable behaviour. Psychotic adolescents should be encouraged to continue their usual educational instruction and social and recreational activities, supplemented by occupational therapy, social skills training, and enhancement of independent self help skills.

REHABILITATION AND LONG TERM CARE

After initial assessment and treatment or discharge from hospital, long term psychiatric care and recurrent hospitalisation are often required. For example, schizophrenic patients will need to continue medication for several months. Most patients are likely to live at home, but there is limited provision of supervised hostel accommodation, group homes, and residential treatment centres for those unable to live with their families. Appropriate educational provisions may be hard to find, especially on a residential basis, although there are increasing facilities for young people with special needs in colleges of further education. Similarly, difficulties may arise in preparing for or re-entering employment. In general, facilities for rehabilitation and long term care are unsatisfactory. Overlap with adult psychiatric services is often inadequate and unplanned and the special needs of chronically mentally ill adolescents and young adults may be overlooked.

MANAGEMENT ISSUES CAUSED BY PSYCHOTIC ADOLESCENTS

Problems arising in the inpatient management of psychotic adolescents, particularly in general purpose psychiatric units, need to be understood by all adolescent health care personnel. They illustrate those problems that are generated in any treatment setting where there is a need to integrate and treat a few odd, sometimes frightening, young people with others, whose disorders are more comprehensible and readily treatable.

Differing staff attitudes towards the concept of psychosis can create difficulties in constructing realistic treatment objectives. Even diagnosis may be emotive because of fears about 'labelling' devaluing the patient and reducing treatment to empirical medication. While outside hospital preconceived ideas about such diagnostic labels as schizophrenia can be unfavourable, staff misapprehensions about the clinical value of diagnosis have to be resolved. In the psychoses in particular, patient care needs the benefit of all available knowledge about course and prognosis. Diagnostic formulations that deflect attention from the possible seriousness of disorder do patients and relatives a dis-service.[21] Lack of a working diagnosis compounds the difficulties of coping with clinical ambiguity, leading to uncertainty about therapeutic objectives and loss of direction in management. Inconsistent staff responses follow, heightening confusion for patients and parents.

Division of opinion in the treatment team may concern how far psychotic behaviour can be controlled by the individual patient and the applicability of ordinary, age appropriate expectations of teenagers. In this respect, it is crucial to prevent the isolation of psychotic adolescents from their peers and to face them with expectations that are compatible with their prevailing level of function. The use of psychotropic drugs may be controversial if medication is construed simply as an expedient way of achieving control, without understanding the problem. The form and consistency of staff responses needs consideration. Grossly regressed behaviour, for example, can generate irritation, rejection, and even a punitive approach. Although an overtly confused, dependent adolescent may evoke caring, protective feelings, difficulties may arise in responding to aggressive, unpredictable, and inaccessible patients. Such young people require close involvement, but impaired contact with reality may be alienating to inexperienced staff and it is helpful if senior staff have had experience with adult psychotic patients.

Consideration needs to be given to the effect on the psychotic patient of being in a busy, high turnover unit, where most patients expect a short stay. The effects of a long stay in this setting can be adverse and it may be impossible to create the stable atmosphere conducive to rehabilitation for the patients who need extended treatment. Reactions of the main group of adolescents to their psychotic peers cannot be overlooked, as strange behaviour may be frightening and evoke rejection or teasing. Invariably, however, problems settle after explanation and reassurance. The essential 'normality' of other patients and the mutual acceptance that usually prevails are valuable therapeutically for psychotic patients. Occasionally, complaints and fears are expressed by parents of non-psychotic patients.

Prognosis

Even after prompt, vigorous treatment most adolescent psychotics are likely to display a chronic, fluctuating course. Length of stay in hospital is likely to be longer than for other diagnostic groups.[22] This is particularly the case in schizophrenia and allied disorders, which may progress to a chronic stage characterised by negative symptoms, such as apathy, paucity of speech, and blunting of affect. In schizophrenia, favourable prognostic pointers include acute onset, associated acute stress, affective features, higher intelligence, and good premorbid personality. In general, the younger the onset, the worse the prognosis.[23] Adolescents with affective disorder are at risk for further episodes, especially if they displayed a bipolar or psychotic clinical picture.

Conclusions

Adolescent psychoses make up a small, but challenging, part of the work of adolescent psychiatric services, which can be overshadowed easily by the bulk of the work with less severe forms of disturbance. Psychotic disorders can be managed effectively in mixed, short stay general purpose psychiatric units, without impairing the treatment of other patients, provided the operational policy is planned for their reception. All staff in adolescent services should be able to cope with the ambiguity created by the uncertain causation of the psychoses, the need for empirical treatment, and the prospect of poor outcome. Early identification and diagnosis is essential and prognostic pointers need to be taken seriously. Over-optimism about outcome, because adolescence is a time of change, can be misplaced.

Adolescent services should give priority to the management of psychotic disorders and no adolescents, under the age of 16 years at least, should be admitted to adult mental hospitals because of lack of facilities or unduly selective admission policies of available adolescent units. Adolescents who relapse or deteriorate insidiously and are destined to become 'new chronic' patients need special attention, in hospital and the community, because existing continuing care and rehabilitation facilities are inadequate. Research priorities include both prospective studies to clarify the natural history and to establish predictors of outcome and the investigation of precursors of adult onset disorders.

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REFEREES AND STAFF

Our referees

Submitted manuscripts are initially seen by the editors or associate editors who then send them to one or two expert advisers for assessment. We thank the following people who kindly reviewed papers for our journal between September 1990 and September 1991. Their expertise and the time so generously given have been a major factor in maintaining high standards.

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Staff changes

We welcome two new associate editors whose experience spans the wide fields of child health and paediatrics and who have additional special interests. Dr D P Addy is a consultant paediatrician at Dudley Road Hospital, Birmingham, and he has a special interest in neurology. Dr H Marcovitch is a consultant paediatrician at Horton General Hospital, Banbury, and he has the ability to evaluate social and emotional problems with clarity.

We thank Professor J K Lloyd, Professor N McIntosh, Dr P J Milla, Professor P O D Pharoah, Dr J F N Taylor, and Dr R M Winter who have completed their periods of office as members of the editorial committee, for their conscientious and meticulous work for the journal. We welcome the following as new members of the editorial committee:

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LETTERS TO THE EDITOR

Tests for growth hormone secretion

Sɪʀ,—We were interested in the correspondence between Dr Addy and Professor Brook and Dr Hindmarsh on detecting organic illness through assessment of height velocity.[1 2] The question, however, is academic and their arguments theoretical since, as we have recently shown, the assessment of height velocity in individuals is so imprecise as to be clinically meaningless. There is effectively no correlation between successive velocities, so that a 12 month velocity cannot possibly identify anyone.[3 4]

The Wessex Growth Study provides a practical demonstration of the problem. Thirty (17%) of the original cohort of 174 school entrants below the third height centile had identifiable organic disease. Eighteen of these were monitored over a period of three years alongside a cohort of 78 short 'normal' children in whom all pathology had been excluded. The height velocity of four of the short 'normal' children and two of those with organic disease was deemed to be on or below the third centile for velocity after the first year. Over the next 12 months, two of the short 'normal' subjects, and three of those with organic disease, were growing at a rate below the third centile, but the identity of the 'poor growers' changed from year one to year two.

We should abandon the notion that low 12 month velocities will effectively identify pathology. The children in the Wessex Growth Study with organic causes of short stature were identified at the beginning of year one on the basis of height screening alone.

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1 Brook CGD, Hindmarsh PC. Tests for growth hormone secretion. *Arch Dis Child* 1991;**66:** 85–7.
2 Addy DP. Tests for growth hormone secretion. *Arch Dis Child* 1991;**66:**749.
3 Voss LD, Bailey BJR, Cumming K, Wilkin TJ, Betts PR. The reliability of height measurement. *Arch Dis Child* 1990;**65:**1340–4.
4 Voss LD, Wilkin TJ, Bailey BJR, Betts PR. The reliability of height and height velocity in the assessment of growth (the Wessex Growth Study). *Arch Dis Child* 1991;**66:**833–7.

The reliability of height and height velocity in the assessment of growth

Sɪʀ,—Voss *et al* make a good point when they emphasise the fact that height velocity is much worse affected by measurement error than height itself, partly because it involves two measurements both subject to error and partly because the normal variability of the error free quantity is much smaller.[1] But it is not clear that their conclusion follows, that velocity charts are no more discriminating than height charts in the screening context that they consider. To establish such a conclusion it would be necessary to have information not only on the normal children on which the charts are based but also on the abnormal children that the screening exercise is intended to detect.

Growth standard charts can be described as providing age specific normal ranges or reference values and their properties need to be assessed in terms such as sensitivity, specificity, and predictive values that are familiar in discussions of these topics. When only a single measurement is available it is usual to express it as a centile position on the height chart and to investigate the child if this position is below an arbitrary level, commonly the third centile. Such a procedure provides a protection against false positive errors; if applied to children from the normal population it ensures that not more than 3% of them will be unnecessarily investigated. It says nothing about the frequency with which children who are genuinely growth retarded will be missed by the screen. It is important to notice that the chart provides centiles for the *measured* height; the 'true' height of a child does not enter into the argument.

Exactly the same considerations apply to growth velocity. If children whose *measured* velocities fall below the third centile on the velocity chart are investigated, only 3% of those from the normal population will be included. Once again, the number of abnormal children picked up by such a screen is unknown, and once again the fact that a child's 'true' velocity may be rather far above (or below) its measured value is not to the point.

Only studies which include children known to be abnormal are capable of distinguishing between the properties of rival screening methodologies. It is natural to suppose that the two measurements included in a velocity are capable of providing more information than a single measurement; the question is whether the value of the extra information outweighs the delay which its acquisition involves.

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Mr Bailey and Ms Voss comment:

Professor Healy is right to stress that velocity could, in some cases, be a useful discriminator in a screening context, but in our paper we were concerned mainly with the estimation of height velocities, and we showed that the imprecision attached to these estimations can be considerable. Unfortunately, disease specific growth charts are rare and more are needed. In the case of Turner's syndrome such a chart is available and the mean velocity is shown to be lower than normal.[1 2] If one were to screen for the disease by identifying all girls with a velocity less than the 3rd centile on the normal velocity chart, between the ages of 5–6 years, this would locate about 25% of girls with Turner's syndrome. On the other hand, screening for those below the 3rd centile for *height*, using the normal height chart at age 5 years, would pick out over 50% of these girls. (Actually, screening by height and then by velocity would be even better as girls with Turner's syndrome are on average shorter than normal and they also fall further behind with increasing age. As Professor Healy points out, however, the extra information gained may not be worth the delay involved.)

The problem of choosing an appropriate method of screening is further demonstrated by our letter in this issue regarding the comments of Dr Addy.[3] In this, we describe how children in the Wessex Growth Study with pathology could not be distinguished from healthy children by their velocity over a single 12 month period. Certainly much work is yet to be done, and data collected on a variety of organic diseases, before it is possible to evaluate rival screening methodologies.

1 Lyon AJ, Preece MA, Grant DB. Growth curve for girls with Turner's syndrome. *Arch Dis Child* 1985;**60:**932–5.
2 Ranke MB, Pfluger H, Rosendahl W, *et al.* Turner syndrome: spontaneous growth in 150 cases and review of literature. *Eur J Pediatr* 1983;**141:**81–8.
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Terbutaline powder in asthma exacerbations

Sɪʀ,—Inhaled β_2 agonists are the most efficient means of relieving acute bronchoconstriction in asthmatic children. However, inhalation technique with a metered dose inhaler is often unsatisfactory particularly in young dyspnoeic children. Spacers have been shown to be useful in this setting.[1 2] Asthmatic children may be reluctant to carry spacers during daily activities because they are cumbersome. The Turbuhaler (Astra, Turbohaler in the UK) is a new multidose breath actuated pure powder inhaler available for the administration of terbutaline. It can be triggered by an airflow of 22 l/min; this is reached by almost all children over 5 years old in a stable condition and even by those with moderately acute asthma.[3] Terbutaline given with a Turbuhaler is effective in the treatment of exercise induced asthma.[4] It has not been reported yet if terbutaline with Turbuhaler is effective in children with acute asthma.

Twenty two children attending the hospital with acute wheeze were included in an open, randomised, parallel group study comparing the efficacy of 0·5 mg of terbutaline given either with a Turbuhaler or with a metered dose inhaler attached to Nebuhaler (Astra). Administration of the drug was carefully supervised and consisted of one inhalation by the Turbuhaler or two consecutive puffs of terbutaline introduced separately by the Nebuhaler at one minute intervals as previously described.[1 3] Before, 15 and 30 minutes after treatment we measured specific airway resistance (sRaw in cm H_2O/l/s, body plethysmograph 2800, Physiosystem), forced expiratory

Results in efficacy of the two systems after inhaling 500 µg of terbutaline. Results are mean (SD)

Variable	*Nebuhaler*	*Turbuhaler*
sRaw (cm H_20/l/s):		
Initial	14·1 (3·5)	13·5 (3·4)
15 Minutes	7·4 (2·0)	6·4 (1·6)
30 Minutes	6·5 (1·7)	6·4 (1·9)
FEV$_1$ (ml):		
Initial	1200 (390)	1610 (510)
15 Minutes	1530 (640)	1820 (610)
30 Minutes	1560 (600)	1830 (580)
PEFR (l/min):		
Initial	184 (47)	217 (74)
15 Minutes	214 (56)	265 (75)
30 Minutes	233 (54)	276 (85)

volume in one second (FEV$_1$ in ml, Pulmonet, Physiosystem), peak expiratory flow rate (PEFR in l/min, mini Wright), heart rate (pulses/min). Results as mean (SD) were compared by analysis of variance. The two groups (11 in each) did not significantly differ in age (Nebuhaler: 8·5 years, range 4·5–13 and Turbuhaler: 10 years, range 6–14). There was no difference between the baselines for any variables. Results in efficacy are presented in the table. Both treatments were effective at 15 minutes to improve lung function compared with baseline ($p<0·01$ for all variables) with little further improvement at 30 minutes. No difference between treatments could be demonstrated at any time for these variables. No cardiovascular effect was observed in the Nebuhaler group. In the Turbuhaler group, a slight increase in heart rate (median:80 to 86 pulses/min) was observed.

In conclusion, inhalation of terbutaline via Turbuhaler gave similar increase in lung function as a metered dose inhaler plus Nebuhaler in children above the age of 5 years with moderately acute exacerbation of asthma. The Turbuhaler is easy to use and to carry and can be recommended for paediatric use.

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1 Pool JB, Greenough A, Gleeson JGA, Price JF. Inhaled bronchodilator treatment via the nebuhaler in asthmatic patients. *Arch Dis Child* 1988;**63**:188–91.
2 Benoist MR, Rufin P, De Blic J, Scheinmann P. Nebuhaler in young asthmatic children. *Arch Dis Child* 1988;**63**:997.
3 Pedersen S, Hansen OR, Fuglsang G. Influence of inspiratory flow rate upon the effect of a turbuhaler. *Arch Dis Child* 1990;**65**:308–10.
4 Lopes Dos Santos JM, Costa H, Stahl E, Wiren JE. Bricanyl turbuhaler and ventolin rotahaler in exercise-induced asthma in children. *Allergy* 1991;**46**:203–5.

Evaluation of a pen injector system for growth hormone treatment

SIR,—We agree with many of the comments of Gluckman and Cutfield about convenience and compliance using a pen injector system (0·5 unit increments up to a maximum of 4·0 units per injection) and the important role of a nurse educator.[1] The authors have demonstrated that if convenient doses of growth hormone using a pen injection system are administered, such as 2 or 4 units (which by serendipity fit the 0·5 unit increments and divide into 16 with no residual) then indeed this pen system is accurate and efficient. However the authors have convincingly argued that traditional fixed dose regimens of 4 units three times a week are obsolete and that the dose of growth hormone should be related to the patient's size. If the dose schedule of growth hormone is related to either weight or surface area, then usually the resulting dose will not be convenient using this pen injector system, which may lead to wastage of growth hormone at the end of the cartridge vial. After four growth hormone injections of 3·5 units, what happens to the 2 units remaining in the cartridge vial?

Dosage for small children may prove difficult, because of 0·5 units per increment dose selection. For example, a child of 0·6 m^2 treated with a physiological replacement regimen of 15 units/m^2/week as a daily injection, will necessitate large steps in dose schedule. The difference between 1·0 and 1·5 units per injection is the equivalent of dosages of 11·5 and 17·5 units/m^2/week respectively, which makes an accurate dose schedule impossible to administer. Of course, there remains the possibility of having varying doses on different days of the week, but this would probably be counterproductive for both convenience and compliance. Although the optimum dose regimen for growth hormone administered during the pubertal growth spurt is unknown, many authors have recommended an increase in dose.[2] The limitation of this pen system to a maximum of 4 units per injection makes a daily regimen of 20 or 30 units/m^2/week difficult to achieve in pubertal children. In a similar fashion, pharmacological doses of growth hormone using such a pen system for girls with Turner's syndrome will have severe limitations; because of the restriction of maximum dose, a schedule of 30 units/m^2/week will restrict the use of this pen system to a child of less than 0·93 m^2 surface area.

We agree that pen injection systems are a considerable advance in convenience to patients. However, if optimum treatment regimens are prescribed, these should not be introduced in a system with inflexible dose selection which may be detrimental to accurate dose schedules and potentially wasteful of expensive resources.

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1 Gluckman PD, Cutfield WS. Evaluation of a pen injector system for growth hormone treatment. *Arch Dis Child* 1991;**66**:686–8.
2 Vanderschueren-Lodeweyckx M, van den Broeck J, Wolter R, Malvaux P. Early initiation of growth hormone treatment: influence on final height. *Acta Paediatr Scand* 1987;**337** (suppl):4–11.

Dr Cutfield and Professor Gluckman comment:
Sister Hamill and Dr Stanhope appear to have misinterpreted the major theme of our paper. We addressed patient perception and satisfaction of growth hormone delivery systems, not growth hormone dose regimens. Publications to date have largely ignored patients' perception of growth hormone delivery. As the primary goal of growth hormone treatment is to promote greater psychosocial wellbeing, achieved in part by attempting to increase adult height, it is essential to consider patient acceptance of the method of treatment. In our study most children and their families preferred a pen to a syringe delivery system. As children self administered at an earlier age with the pen than with the syringe, we presume these are real differences perceived by the patients. If the prime motive of treatment is the improvement in psychosocial wellbeing, then use of the injector pen, despite a minor compromise in dose regimen, must be considered by the physician in the choice of treatment modality.

If there is a real advantage to the extreme accuracy of the regimens proposed by Hamill and Stanhope, hopefully pharmaceutical companies will respond by producing vials of varying growth hormone concentrations to allow more precise titration of dose using pens or other easy use administration devices.

Day case ligation of patent ductus arteriosus in preterm infants

SIR,—I read with interest about the brave new world of day case ligation of patent ductus arteriosus (PDA) in preterm infants[1] and was relieved to learn that infants were not discharged home on the day of surgery. The authors are to be commended on developing a safe and efficient service but are not justified in concluding in their abstract that 'if it is carried out early [ligation of PDA] will reduce the time before extubation and discharge from the intensive care unit'. They present no control data to support this conclusion. Indeed they refer in their discussion to a multicentre comparative study which showed no significant difference in mortality, duration of respiratory support, and number of days in hospital between infants receiving medical or surgical treatment.[2]

My own experience (also uncontrolled) over the last 10 years in a neonatal intensive care unit serving approximately 5500 births a year is that surgical ligation of PDA in preterm infants is very rarely necessary, only one infant having been operated on in the neonatal period. During this time we cared for 492 infants of birth weight ≤1500 g of which 173 had birth weight ≤1000 g. Our survival rates compare favourably with the other four large Trent region centres,[3] and long term ventilation (beyond 14 days) is now rarely needed.

Fluid restriction, early use of indomethacin, effective treatment of underlying lung disease including dexamethazone, and above all patience will allow the preterm infant's duct to close in all but exceptional cases. I am very worried at the apparent early resort to surgery which many appear to adopt.

It is not enough to show an operation is safe and readily available, it must also be shown to be necessary.

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1 Satur RM, Walker DR, Dickinson DF. Day case ligation of patent ductus arteriosus in preterm infnats: a 10 year review. *Arch Dis Child* 1991;**66**:477–80.
2 Gersony WM, Peckham GJ, Elisson RC, Miettinen OS, Nadas AS. Affect of indomethacin in premature infants with patent ductus arteriosus: results of a national collaborative study. *J Pediatr* 1983;**102**:895–906.
3 Field D, Hodges S, Mason E, Burton P. Survival and place of treatment after premature delivery. *Arch Dis Child* 1991;**66**:408–11.

Drs Satur and Dickinson comment:
As cardiologists and cardiac surgeons at a supraregional centre for paediatric cardiac surgery we see a highly selected group of preterm infants with a patent arterial duct, namely those referred by paediatricians specifically for ligation of the duct because the measures suggested by Dr Dodd had either failed or were considered inappropriate. Our conclusions at the end of the paper relate only to this group of patients. We have shown that if a paediatrician feels that active surgical management of the duct is necessary he or she should not delay because of the perceived hazards of transportation and operation. However we would agree entirely with the statement that the operation must be shown to be necessary. Because of the selected nature of our patients we cannot address the wider issues relating to the management of the patent arterial duct in the neonatal unit. We

are aware of differing rates of referral for ductal ligation from neonatal units within our own catchment area, but whether this is the result of different management or different case mix is uncertain. The statement in the abstract is, we agree, not supported by a controlled study, which we are not in a position to perform.

Absent or reversed end diastolic flow velocity in the umbilical artery and necrotising enterocolitis

SIR,—We read the paper of Malcolm *et al* with interest, and noted the close association between absent or reversed end diastolic flow (AREDF) velocities in the umbilical artery in high risk pregnancies and neonatal necrotising enterocolitis.[1] We wish to add some data that supports the hypothesis that it is AREDF, independent of growth retardation and prematurity, which predisposes to necrotising enterocolitis.

A prospective study of all patients attending a high risk fetal assessment clinic was performed over a two year period in this hospital. Umbilical artery flow velocity waveforms were studied using a Doppler Mark V Duplex scanner in pregnancies complicated by hypertension and/or intrauterine growth retardation. There were 20 cases where AREDF was identified in the umbilical artery of a morphologically normal fetus; of these, two were intrauterine deaths. The 18 liveborn fetuses were matched for gestational age and birth weight with 18 liveborn fetuses from the same cohort who had never had AREDF. The mean (SD) gestational ages were 32·2 (2·9) and 32·6 (1·9) weeks respectively for cases and controls and mean (SD) birth weights were 1323 (544) and 1489 (386) g. The mortality rate was 30% (6/20) for fetuses with AREDF; none of the controls died. Necrotising enterocolitis (defined as clinical features suggestive of necrotising enterocolitis confirmed by radiological evidence of intramural or portal air) occurred in four (22%) of the babies who had had AREDF compared with one (6%) of the control babies.

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Body water measurements in growth disorders

SIR,—The ability of bioelectrical impedance to estimate body composition in the paediatric population is a subject of burgeoning interest. Two equations have now been published that relate height^2/impedance (H^2/I) to total body water by simple regression equations.[1 2] It is noteworthy that these two equations, based upon children with large variations in height, weight and age, are remarkably similar and this has led us to combine the raw data.

The new regression equation is therefore: total body water (litres)=$0{\cdot}13+0{\cdot}58\ H^2/I$ with a standard error of estimate of 1·3 litres.

This equation is based on 60 measurements of bioelectrical impedance and total body water using $H_2{}^{18}O$ isotopic dilution in children aged 5·2 to 17·9 years. It is hoped that this equation may be of use to those using impedance techniques in children.

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1 Davies PSW, Preece MA, Hicks CJ, Halliday D. The prediction of total body water using bioelectrical impedance in children and adolescents. *Ann Hum Biol* 1988;15:237–41.
2 Gregory JW, Greene SA, Scrimgeour CM, Rennie MJ. Body water measurements in growth disorders: a comparison of bioelectrical impedance and skinfold thickness techniques with isotope dilution. *Arch Dis Child* 1991;66: 220–2.

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